"BERI-BERI"

being

A Thesis submitted for the degree of

M.D. of the University of Edinburgh,

by

Edward Laidlaw Thomson,

M.B., Ch.B., ~~M.R.C.P.(Edin.)~~

Surgeon Lieutenant, R.N.V.R.

April, 1943.

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PREFACE.

Beri-Beri has engaged the attention, at one time or another, of most workers in the field of tropical medicine. In the past, interest centred round the problem of the aetiology of the condition. During recent years, research has been concerned with the biological significance, the chemical structure, and the methods of estimation of vitamin B_1 and other essential food factors.

My personal interest in beri-beri has been, to a great extent, clinical. The pages which follow have been devoted mainly to a description of the history, the evolution of our modern theories regarding the action of vitamin B_1, a survey of the condition itself with remarks chiefly directed to the symptomatology, diagnosis, and treatment, and to recommendations for the future eradication of the disease.

The observations I have recorded have been taken from five years of medical practice in Singapore, during which time I was fortunate enough to have entire control of an "outbreak" of beri-beri, affecting ratings of the Straits Settlements Royal Naval Volunteer Reserve. Many copious notes and photographs were taken at the time - these were unavoidably lost, and lie at the bottom of Banka Strait. As a result, the author has been forced to draw from memory for his subject matter.

Personal observations and conclusions are contrasted with the opinions expressed in the more important articles sifted /

sifted from the multitudinous array of literature. An attempt has been made to balance them; apparent differences have been recorded, and where possible reconciled.

There is possibly no other subject where so many contradictory statements have been made; nevertheless the whole is a most inspiring story, where the ultimate destination has been reached only by long, laborious travel.

This thesis is entirely my own conception. I am however, indebted to Messrs. John Bale Medical Publications for permission to use the illustrations, and to Miss Charlton of the Central Medical Library for her help in unearthing the relevant literature. I would also like to express my warmest thanks to Miss MacGregor, W.R.N.S., for her assistance in typing the manuscript.

ETYMOLOGY.

The derivation of the word Beri-Beri is shrouded in mystery.

Bontius and Meyer-Ahrens believed it to have come from a Hindustani word "Bheree", meaning sheep, from the somewhat fanciful resemblance of the gait of persons so afflicted to that of sheep.

Herklots suggested another Hindu word "Bher-Bheri" which signifies a swelling.

The Sudanese word "Biribi" was thought of by Platteeuw: it means stiff walking.

Carter claimed that it was derived from the Arabic words "Buhr" (asthma) and "bahri" (a sailor).

However, the consensus of opinion would indicate the true derivation to be Cinghalese: "beri" signifying weakness, and by reduplication, great weakness.

In 1913 Vedder stated that "It is impossible to definitely trace the origin of the word, but it is undoubtedly an oriental word, and probably from some language allied to or derived from Malay."

On further investigation I find that, until the "English" term "sakit biri-biri" was adopted, there was no special name for it in Malay. Prior to this the Malays had spoken of "sakit basal", or "sakit bengkak-bengkak" to indicate dropsy of any origin. "Sakit sebar" or "sakit lumpok" was applied to numbness of the limbs - probably dry beri-beri. /

beri-beri.

At the present time, Malays talk of "Biri-Biri kering" (dry Beri-Beri) and "kaki-bengkak" (wet Beri-Beri: lit. swollen legs).

The Cinghalese derivation therefore seems to be the one of preference.

HISTORY.

A study of the history of Beri-Beri cannot fail to impress the investigator on account of the magnificent work which has gone to further our knowledge of this interesting and intriguing illness.

Much has accrued from closer contact with the Eastern hemisphere: new chapters of medicine have been opened up, among them, that of the deficiency disorders, a chapter which some day may be regarded as equalling in importance the discovery of micro-organisms as causative factors in disease.

Independent nutritional studies in the West might have unraveled the tangled skein of these disorders without referring to the East, but it is most improbable that interest would have been so well sustained without the picture before us, of a dramatic disease of dietary origin, affecting the teeming population of the Orient.

I am unable to verify the supposedly earliest reference to beri-beri. Many recent works state that according to MacGowan, (1), the first reference to the condition is to be found in the Neiching, attributed to Hwangti (B.C. 2697). Beri-Beri was quite possibly prevalent in China at this time as customs, food and conditions of life have changed little with the passing centuries. The only reference however, I can find in any of MacGowan's works to early medicine in China, relates that Shen-nung (B.C. 2737 - 2697) is worshipped as the God of Medicine, and that a pharmacopoeia which is in use at the present time is said to have been written by him. Hwangti (B.C. 2697 - 2597)

followed /

followed Shen-nung as Emperor, but does not appear to have been particularly interested in medicine.

The Kinki (golden chest) written about 200 A.D. by Chochiyukei is said to contain a few prescriptions for beri-beri, (31).

The Romans seem to have been aware of the condition in 24 B.C. as, according to Meyer-Ahrens, it is described by Strabo and Dion Cassius that the armies were affected by it during the campaign in Arabia.

There is a remarkably clear account of beri-beri, referred to as Kakke, in the Senkinho (thousand golden prescriptions) written by Sonshibaku in 640 A.D., and it is interesting to note that the illness was believed to be "produced by a gaseous poison" which "originates in the earth".

Most of the early Japanese writers appear to have obtained their information from Chinese sources, and there is no accurate description of the condition until 1720 when the Koyoigen (prescriptions from a physician's leisure hours) was written by Kagawa Shuan.

Scott, (2), has found a reference in a statement by Villalabos, Spanish Governor of the Phillipines, who wrote in 1543 as follows:

"The people began to get sick and to die immediately .. ..after gradual swelling, especially annoying the abdominal region. For the illness which they called ber-ber, no remedy could be found."

For the past three centuries, the name of Jacobus Bontius (1592-1631) has been revered in Holland, as the father /

father of tropical medicine.

In his "methodus medendi" and "observationes", (3), he gives a clear description of dry, atrophic beri-beri, and the hydropsy: indeed following an attack of dysentery, he himself suffered from the disease and it is not improbable that he actually died from it. He believed the cause of the disease to be "principally a thick and sluggish phlegmatic humour derived from the nocturnal dampness."

From Ceylon in 1808, came Roger's description of Asthmatic Hydrops, (4), which the natives called beri-beri.

Then in 1835, Malcolmson, (5), observed the transformation of wet beri-berics into dry, after sudden diuresis, and that the dry type not infrequently later developed oedema. He therefore concluded that both forms were manifestations of one and the same disease.

Speculation has been rife throughout the ages as to the cause of beri-beri: thus we have Heymann from Java in 1855, postulating that it was merely another manifestation of malaria. This was only natural, in that beri-beri not infrequently occurs along with malaria, and commonly is a sequel of any debilitating illness in the tropics.

Evezard of Madras in 1862 believed it to be a kind of Pernicious Anaemia. It was only a few years prior to this account, that Addison had described the anaemic syndrome, and, as we now know, tropical macrocytic anaemia is a not uncommon concomitant of beri-beri.

In 1878, Gelpke compared beri-beri with Trichiniasis, but instead of measly pork, the food conveying the infection was /

was thought to be dried fish, which entered largely into the diet of prisoners in the East.

In 1882, Erni regarded, what he imagined to be Trichiuris Trichiura, as causative: there is little doubt, however, that hookworm was what he observed. I have myself suffered from Ankylostomiasis and much of the symptomatology is similar to that of beri-beri.

One of the earliest advocates of the dietary theory of the origin of beri-beri was the Surgeon-General of the Japanese Navy, Takaki, (6). As a result of his recommendation in 1882 that meat and legumes should be added to the navy diet, and later that a partial substitution of barley for rice should be practiced, the incidence of beri-beri, which in the Japanese fleet had varied from 23% to 40% of the entire force, fell to less than ½%, and has been negligible ever since.

It was then thought that beri-beri was caused through an insufficiency of protein in the diet. This theory, however, became untenable following the outbreak in the Norwegian fishing fleet in 1894. Prior to this, the men had been subsisting on rye bread, legumes and pork - but it was considered advisable to "improve" their diet by the substitution of preserved meats, salted fish, and white bread; the result was, of course, the introduction of ship beri-beri.

Much of the credit for the advancement in our knowledge, and for a specific hypothesis as to the cause of beri-beri, must go to the Dutch.

In 1886, a government commission was created in Java, /

Java, in order to investigate the cause of the increase in the incidence of beri-beri in the Dutch army, at that time engaged in the Achin war. Pekelharing and Winkler reported that "from the blood of beri-beri patients, a microbe could be cultivated, which, if injected into rabbits, caused degeneration of the nerves, which could be considered to be analogous to that found in the corpses of beri-beri patients." Their recommendations proved to be useless. However, from the same laboratory in 1897 came a report on "Polyneuritis in Chickens" by Eijkman, (7), who demonstrated that a paralytic condition resembling beri-beri could be developed in fowls by feeding them upon an exclusive diet of polished rice.

As so often happens, this important discovery resulted from mere chance. Avian beri-beri developed spontaneously among chickens, which were cooped up at the laboratory, in the course of studies which were intended to demonstrate the infectious character of the disease.

Eijkman then performed a series of experiments which served to shew that the condition ensued, or failed to appear, according as the birds were fed on polished or unpolished rice. In this way, the deficiency theory of the origin of beri-beri came to be definitely formulated. Eijkman did not go unrewarded. As a result of his researches, he was, together with Professor Gowland Hopkins, in 1929, awarded the Nobel Prize.

To complete this part of the story - following the work of Eijkman and his successor, Grijns, General van Heutz /

Heutz on Achin at once put an end to "life in the concentrated line" - overcrowding was stopped, food supplemented by fruits and herbs, and beri-beri from that time decreased.

In 1901, following the advice of Grijns, Hulshoff-Pol, (8), conducted a series of experiments at the Buitenzorg asylum. He added 150 gms. of Kachang Hijau (green dhall) each day to the white rice which he gave to a group of 78 natives. To another group of 222 natives he gave only white rice. Of the former, none developed beri-beri, but of the latter, 68 cases occurred in three months. He then demonstrated that by adding 50 - 100 gms. of Kachang Hijau daily to the diet of those afflicted, he was able to cure the condition.

About this time, there were many authorities who subscribed to a toxic cause of the condition.

For instance, Rees in 1898 noted that beri-beri occurred in outbreaks where there was overcrowding and remarked that removal from an "infected" environment such as leaving ship and entering hospital was followed by rapid improvement and recovery; unfortunately he overlooked the fact that this implied in most cases also a change of diet.

Carpenter, who had a wide experience of the disease in British North Borneo, wrote that "there is a germ in the soil of the district where beri-beri is endemic, that may actually, per se, cause the disease in predisposed subjects."

Clark in 1899 from Hong Kong reported what seemed to be incontrovertible evidence in favour of the infection theory. The children from an asylum for the blind attended divine worship at a neighbouring home for foundlings. A few of the /

the children from the asylum were beri-berics. In five months time, 62 out of 102 children in the foundling home were found to have beri-beri.

Hamilton Wright, (9), in 1902 went further when he stated that "there can be little doubt that the focus of the activity of the causal organism of beri-beri is in the stomach and upper part of the small gut.....It may be predicted that when the causal organism is isolated it will be found to present many of the characteristics of the Klebs-Loeffler bacillus."

In the same year, arsenic was mentioned as the probable causative factor. The outbreak of peripheral neuritis in England during the years 1900 - 1901 suggested this possibility to Ross who found arsenic in the hair of twenty-one cases of beri-beri in Penang and Singapore.

Hamilton Wright, however, observed that coolies, working in cuttings and at mine stripping where they were exposed to lodes containing anything from 10% - 50% arsenic, (e.g. at Chankat Pari) escaped beri-beri; also that the outbreaks occurred in prison where no arsenic could have entered. These findings led him to write that "It appears to me to finally exclude arsenic as the cause of beri-beri."

Manson, also in 1902, postulated that beri-beri was caused by

"(a) a toxin,

(b) the product of a germ operating in

(c) some culture medium,

(d) located outside the body.

Further /

Further that:-

(e) the said toxin enters the body neither in

(f) food,

(g) nor water, and I am thereby forced to conclude that it is introduced

(h) through the skin, or

(i) that it is inhaled."

Tsuzuki in 1905 claimed to have discovered from the urine and faeces of patients, the causative organism, which he called the Micrococcus Beri-Bericus. Later he added that agglutination reactions had been observed in 97% of cases, and that injections of the soluble toxin of his organisms produced, in experimental animals, symptoms and signs identical with those met with in human beri-beri.

We thus see how, in the opening years of the present century, the question of the cause of this disease was in a very nebulous state; we note also how scant was the attention paid to Takaki's dietetic reform, and to Eijkman's deficiency theory. It was not until Fletcher of the Institute of Medical Research, at Kuala Lumpur in 1905, (10), and Fraser and Stanton in 1909 - 1910, (11), (12), (13), published their studies of the human disease in Malaya, that this view as to the aetiology caught hold outside the Dutch Colonies.

Between the years 1891 and 1910, 17.3% of all hospital admissions in Malaya were cases of beri-beri. Pudoh Gaol in Kuala Lumpur was the "home" of beri-beri at this time, and it was, to a great extent, the result of Stanton's dietetic reform, that control was achieved.

Fletcher, as the result of experimental work carried /

carried out on inmates of the Kuala Lumpur Lunatic asylum, concluded that "uncured rice is directly, or indirectly a cause of beri-beri: the actual cause being either

(1) a poison contained in the rice,

(2) a deficiency of proteid matter, the disease being due to nitrogen starvation, or

(3) uncured rice does not form a sufficiently nutritive diet, and renders the patient's system specially liable to invasion by a specific organism."

It had been suggested by Grijns and Braddon that beri-beri arose from too exclusive a diet of rice and particularly of over-milled rice - milling having removed pericarp, aleurone layer, and the germ.

This led to the crucial, critical, and classic experiments of Fraser and Stanton who shewed that

(1) locality had nothing to do with the disease,

(2) contagion played no part,

(3) organismal infection could not be the cause,

(4) there was no evidence of any "beri-beri producing" agent in polished rice.

Then followed research on fowls. One group was fed on polished rice, another on partially husked padi from which the polished rice had been prepared, and a third on polished rice, plus the substances which had been removed by the polishing.

Results proved that polyneuritis in birds was due to consumption of rice from which the pericarp had been removed; furthermore, that polished rice was equally harmful whether it was freshly prepared or had been stored for some time - that is, the /

the development in it of a poison seemed to be excluded.

Other notable research involved three hundred coolies divided between two railroad labour camps. To one group, Fraser and Stanton issued the customary white rice as a staple article of diet; to the other, "cured" rice, which retained a large part of the bran coats, was given. In about three months time, a severe outbreak of beri-beri occurred in the "white-rice" camp, while the "cured-rice" camp remained free from the disease. Later the rice issues were reversed. This was promptly followed by a sharp reduction and disappearance of the disease in the first camp, and the subsequent development of an epidemic in the second.

Stanton concluded that "in the milling and polishing, there is removed from the grain some substance of high physiological importance in metabolism, the absence of which results in polyneuritis in fowls, and beri-beri in man, when a diet is consumed of which white polished rice is the staple. Whether these substances act by rendering other elements in the diet available for nutrition or whether they are themselves the nutritive material necessary for nerve tissue can in our present state of knowledge, only be matter for conjecture."

Based on their researches, Fraser and Stanton indicated preventive means for the use of those whose diet consisted chiefly of rice. The main principle was, of course, to use unpolished rice, bearing in mind the fact that even food and wholesome rice could be rendered productive of beri-beri by improper methods of cooking and preparation. For those using polished rice and developing beri-beri, cure could /

could be obtained, in some cases at any rate, from the use of polishings; but since polishings were usually mixed with dust and other adventitious matter, an extract was prepared of such a strength that 1 c.c. represented the soluble constituents of 10 grammes of fat free polishings. Avian polyneuritis responded to this extract, which proved efficient in prophylaxis and curative in therapy.

This research, which has just been mentioned, is a shining example of meticulous observation, clear deduction, and incontrovertible conclusion.

Apparently Funk, (14), was inspired by Fraser and Stanton, because his early experiments followed along the lines which the latter had pursued. Funk however, boldly projected the deficiency theory as the cause not only of beri-beri, but also of scurvy, rickets and pellagra. The name vitamin(e) which he gave to the exogenous factors believed to be necessary for the prevention of these illnesses was a stroke of genius. He had probably drawn also from Hopkins' work in connection with "accessory food factors" in milk, but a single word such as vitamine proved necessary to focus the attention of observers throughout the world upon the possibilities of the field.

Funk investigated the properties of the vitamin which he had isolated from yeast and analysed it into three different substances, but after trial, concluded that in treatment, the whole should be used.

He /

He continued with his experiments, contrasting diets of high carbohydrate content with others high in fat or protein, and found that the onset of polyneuritis appeared much earlier on the excess carbohydrate diet.

No previous work had demonstrated any relationship between vitamin B requirements and carbohydrate metabolism.

During the war of 1914-1918, the outbreak of beri-beri amongst our troops in the Dardanelles and Mesopotamia led to investigation of the anti-beri-beri content of foods by Cooper, Chick and Hume. In this "epidemic" only British troops were affected. Their diet comprised mainly biscuit, white bread, tinned meat and preserved foods. The Indian regiments, whose diet contained atta, a coarse wheat flour, and dhall, dry pulses, with a high anti-neuritic content, escaped.

Nineteen fifteen saw McCollum, (15), state that "There are necessary for normal nutrition during growth two classes of unknown accessory substances, one soluble in fats.....and the other soluble in water." He termed the first factor present in butter and cod liver oil, "A", and the second, which was to be found in milk, yeast, rice polishings and wheat embryo, "B".

It was soon realised that "water-soluble B" and the anti-beri-beri (or anti-neuritic) factor had similar properties and distribution, and it was assumed that they were identical.

Evidence that vitamin B contained two factors was brought forward in 1920 by Emmett and Luros, (16), and later in 1926 by Smith and Hendrick, (17), who shewed that yeast which had been autoclaved for six hours still retained a growth-promoting /

growth-promoting principle, although such treatment inactivated the anti-neuritic factor. In 1932 the Medical Research Council, (18), recommended the name of vitamin B_1 for the heat-labile anti-neuritic factor, and vitamin B_2 for the heat-stable anti-dermatitis and anti-pellagra factor.

After 1920 efforts were made to isolate vitamin B_1: the first successful result was achieved in 1926 by Jansen and Donath, (19), who obtained 100 mgm. from 3 kgm. of rice polishings.

The following scheme, (20), shews the manner in which the vitamin was isolated.

Rice polishings extract

↓

Adsorption on acid clay

↓

Filtrate ← → Adsorbate

↓

Add $Ba(OH)_2$ solution

↓

Precipitation with $AgNO_3$ + $Ba(OH)_2$

↓

Precipitate ← → Filtrate

↓

Reprecipitation with phosphotungstic acid, chloroplatinic acid, alcohol and acetone, picrolinic acid.

↓

Crude picrolonate of vitamin B_1

↓

H Cl.

↓

Vitamin B_1 Hydrochloride.

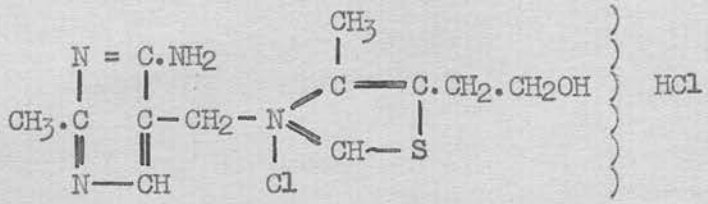
Later in 1935, Jansen, (21), suggested the name "aneurin" for pure B_1. Williams more recently has proposed the alternative name - thiamin, as it contains a thiazole grouping.

In 1932 Windaus and collaborators, (22), isolated the vitamin from yeast and determined the correct empirical formula of the vitamin.

The /

The final chapter in its history was written by Williams and Cline, (23), who brought their work to a brilliant conclusion by the synthesis of vitamin B_1 in 1936.

Chemical structure of Vitamin B_1



After the last war there were still experimentalists who were not convinced that the problem of beri-beri had been solved.

Bernard in 1912 from Saigon, as the result of research which included the isolation of Bacillus asthenogenes from the blood of almost 100 patients, and the production, by its inoculation into pigs, of paralysis in 6 to 7 days, suggested that, though beri-beri was probably to some extent a vitamin deficiency, there was an added toxic factor - that of B. asthenogenes which occurred in soil, and more important, in rice.

Cannon, in the British Medical Journal, 1929, was of the same belief, when he concluded that beri-beri was due to

(1) deficiency of vitamin B.

(2) B. asthenogenes and

(3) endocrine disturbances.

André in 1933, (24), also added weight to this theory when he stated that avitaminosis alone would not explain the disease. "A study of cases" he continues, "as seen, for example in an outbreak at Hankow in 1929, shews clearly that it has the characteristics of an infective malady." He affirmed that three /

three factors were concerned:-

(1) B. asthenogenes.

(2) Gastro-intestinal disturbance, associated with carbohydrate fermentation,

(3) and a lowered resistance.

In 1929, Matsumura and his colleagues, (25) described a B. Kakke which they had isolated from the stools of 74% of cases of beri-beri and stated that it was "the principal aetiologic factor in experimental beri-beri."

de Araujo investigated an outbreak in Bahia, Brazil and concluded that though vitamin B deficiency was not the cause, neither was the organism of Matsumura, judging by agglutination reactions. In 1932, Ramos of Pernambuco sealed the fate of the organism by shewing that 50% of normal sera agglutinated the organism.

McCarrison, (26), was also inclined to believe that there was more in the aetiology than mere vitamin B deficiency. This conclusion was the natural outcome of his observations that, in Madras, the incidence of beri-beri was ten times higher among the users of home-pounded, unpolished rice, than it was among those natives who ate polished rice.

It has since been shewn, however, that the conditions under which rice is grown, in particular, its water supply, are factors in determining the endemicity of beri-beri. Rice grown on puddled fields, whereon a large amount of water is allowed to remain, has nearly $\frac{1}{3}$ less nutritive value than the same rice grown under dry, rain fed conditions.

Japanese authors have reported finding a decrease of vitamin B /

vitamin B in the tissues of polyneuritic birds, but not in human cases: they suggest an intestinal intoxication as did Hamilton Wright, and later Tsuzuki and Matsumura.

Megaw following on Braddon's theory of over thirty years ago, is another who maintains that the vitamin deficiency is only part of the story, that the existing cause is consumption of damaged rice, toxin developing when it is stored in the hot, rainy season.

He concludes that, (27),

"The probable causes are

(1) vitamin B_1 deficiency in the diet,

(2) food intoxication, or

(3) a combination of these two factors.

We thus see how, at the present time, there are still divergent opinions as to the exact interpretation of vitamin deficiency with regard to beri-beri.

The views now held may be summarised and divided into:

firstly: the theory that beri-beri is of an infectious nature, and that deficiency plays an important part, and

secondly: that it is entirely due to lack of specific factor or factors.

Recent work would indicate that beri-beri is very definitely a deficiency disease: there has been but little support for the theory of infectious origin.

It must be emphasised however, that beri-beri is a name which has been applied by use and wont to a condition which occurs in the Far East, and in which certain signs and symptoms predominate. Only recently has it become /

become customary to assert that this syndrome is caused by one, and only one factor - thiamin deficiency. This conception, I believe, essentially to be false.

All of the symptoms which occur in the syndrome called beri-beri can not be attributed to lack of vitamin B_1 alone. I maintain that in nearly all cases, some of the symptoms are caused by deficiency of other components of the vitamin B complex or of other important food factors, - some possibly not yet differentiated.

Synthetic Thiamin produces a rapid cure of certain manifestations of beri-beri but some persist and even become worse.

It has been my practice to exhibit not only vitamin B_1 but also other factors of the B complex, with results which justified this assertion - one must not forget that in certain cases it was necessary to add to the improved dietary, other vitamins apart from the B group.

It is interesting to note that recent observations on induced vitamin B_1 deficiency have shewn that it is impossible to produce beri-beri experimentally in many, by diets poor in vitamin B_1 only.

Williams and his collaborators, (28), observed the signs and symptoms produced in fifteen volunteers, who, for 21 days, were placed on a diet containing less than 0.1 mgm. of vitamin B_1 daily. Anorexia, fatigue, loss of weight, insufficiency of free gastric juice, constipation and tenderness of the calf muscles, were observed in all cases - oedema, cardiac dilatation, and peripheral pain were, however, absent. A further factor of importance was noted: hyperchromic macrocytic /

macrocytic anaemia developed in five out of eleven cases,(29). Electrocardiographic changes were noticed. Blood sugar curves shewed slight impairment of carbohydrate tolerance, but the blood bisulphite binding substances were not abnormal.

As a result of their investigations, Williams and his collaborators concluded that a climatological factor and physical activity may influence the rate of development of vitamin B_1 deficiency. They, moreover, questioned the accepted view that vitamin B_1 deficiency is responsible for the classic features of beri-beri.

Meiklejohn, (30), in addition to Williams, has doubted whether vitamin B_1 deficiency alone, is responsible for many of the features of true beri-beri. He has stated also that vitamin B_1 is necessary for the metabolism of all tissues and not only for nervous tissue and that the vitamin relieves pain by restoring normal metabolic processes in muscle and nerve tissue.

The nervous manifestations of B_1 deficiency which are so dramatic, and the results of therapy, which are so spectacular have however, led to the belief that thiamin is the antineuritic factor.

It is not definitely known for how long the diet must be depleted of vitamin B_1 for the onset of beri-beri to occur, although Vedder, (31), has stated that about three months elapse before symptoms appear.

The following facts have been forgotten in the limbo of the past:

Doctors /

Doctors Travers, Gerrard, Gimlette and Hamilton Wright, between May 3rd, 1901, and April 1st, 1902, examined 1,000 prisoners on admittance to Pudoh Gaol, Kuala Lumpur. No signs of the earliest manifestations of beri-beri were determined in these men, yet amongst them, 90 developed beri-beri to a marked degree, one within 7 days, 10 within 14, 6 within 21 days, and 9 between 30 and 45 days after incarceration, (9).

The disease has frequently been produced in volunteers. Shimazono, (32), describes an 18 year old male who was given a thiamin deficient diet. The results were as follows:-

31st day - anorexia,

32nd day - vomited,

41st day - hyperaesthesia legs,

44th day - oedema ankles,

49th day - knee jerks absent,

70th day - experiment terminated as condition of patient was considered dangerous. Large doses of rice polishings were therefore given, and recovery was prompt, except for sensory and motor changes which persisted for many months.

The seeming discrepancy in these findings depends, I believe, on climatic conditions, the type of diet given, the amount of physical exertion indulged in, and most important of all, the vitamin B_1 content of the diet preceding the experiment, or of the prisoners prior to their incarceration.

It is considered, however, that beri-beri often manifests itself in considerably less than three months. One of /

of the S.S.R.N.V.R. ratings, who on being called up, shewed no sign of incipient beri-beri, nor did he vouchsafe any complaints at the time, reported at the sick bay in 3 week's time - then, an undoubted early case of beri-beri.

Many predisposing factors play a part in the development of the disease. These include fevers and toxaemias, increased physical exercise, pregnancy and lactation, fatigue, hyperthyroidism, digestive disturbances and diseases interfering with the absorption of food, particularly achlorhydria.

Nixon, (33), from Hong Kong has pointed out that many Chinese women appear normal in early pregnancy, but are often "in extremis" towards the end from beri-beri. This also occurred in Singapore, not only in women of the Chinese race, but in Malay and Indian women as well. If it did not occur during pregnancy, beri-beri was often discerned first in the puerperium as a result of the extra strain induced through lactation.

It is also my contention that European women in the tropics shew signs of a partly deficient state not infrequently, when pregnant, and it is a question which should be borne in mind.

Man, as well as experimental animals, is apparently unable to synthesize thiamin, nor can he store it to any great extent. It follows that a person with frank beri-beri undoubtedly has a marked depletion of his stores of thiamin.

It must be obvious that from the state of complete saturation of vitamin B_1, to one of true beri-beri, there is

a /

a range, in which a person may shew signs of incipient deficiency, or may even be free of symptoms, yet subsist on a low intake.

The following factors are of importance in the occurrence of thiamin-deficient states, (34):-

a) a deficiency in the diet,

b) failure of absorption,

c) deficient storage,

d) failure of utilization,

3) increased requirement.

It is my personal belief that beri-beri is a "syndrome deficiency"; that, apart from coincidental (and often predisposing) fevers, infection plays no part in the causation.

What has led so many investigators astray in the past is the fact that there is a very definite association between beri-beri and toxaemia. In other words, many of my patients who developed beri-beri or shewed signs of a partly deficient state, were actually suffering from some other illness at the time, for example common cold, malaria, dysentery, hookworm infestation, and consequently there was increased need for the vitamin which had not been forthcoming.

Vedder, (35), has some interesting views on the causation of beri-beri. His original hypothesis in 1912 was that dry beri-beri was caused by a deficiency of what he called "X" factor and that the wet form was caused by deficiency of "Y". In 1940 he went further by stating that "Deficiency of both (X and Y) produces the mixed disease. When /

When we learned about B_1, we assumed that this was the anti-neuritic vitamin, because it promptly relieved the symptoms of fowls, that had developed polyneuritis after exclusive rice feeding. It is anti-neuritic, but it is even more effective in producing miraculous cures of the wet type of beri-beri. B_1, therefore represents part of X and all of Y..... .....The remainder of X is apparently vitamin A and certain factors of the B_2 complex. When these are deficient, profound degeneration of the entire nervous system is produced, which all observers find cannot be promptly cured by the administration of vitamin B_1. We see, therefore why a complete and adequate diet is the best treatment for these cases, after preliminary treatment with thiamin."

One further factor may be mentioned - rice is clearly the main factor in the causation of beri-beri. Ever since the Federated Malay States and Singapore interdicted the use of polished rice in their hospitals, schools, and gaols, beri-beri has become almost non-existent in these institutions.

It is my firm conviction that despite the similarity between beri-beri and the infectious diseases, despite the apparent "infective endemicity" which McCarrison and Megaw still evidently adhere to, the time will come when all authorities will concur to the deficiency theory. I have attempted to describe in as balanced a manner as possible, the reasons why this theory can be the only one tenable.

Many definitions of the condition have been given.

In /

In the light of present knowledge, the following is suggested:-

"Beri-Beri is a condition which occurs predominantly amongst the rice-eaters of India and the Far East. It is a syndrome characterised by neurological lesions involving particularly the peripheral nerves, by oedema, or by acute congestive heart failure.

In the main, it is occasioned by lack of vitamin B_1; other factors, most important of which are the constituents of the vitamin B complex, are however, involved".

PHYSIOLOGY.

OCCURRENCE OF VITAMIN B_1

Vitamin B_1 is present in many different foods. It is most concentrated in the outside bran coats of grains such as rice, and in yeast: ripe peas and beans are rich sources, and vegetables, fruits and nuts, contain small amounts.

Some micro-organisms are able to synthesize vitamin B_1. Bacteria, for example, in the large bowel of nursing children, in the intestinal tract of cattle, sheep and rats, have this power, (36), (37).

The vitamin is widely distributed in animal tissue such as the liver, kidneys and muscles - especially in the heart. The actual amount is, however, exceedingly small: storage of large amounts does not take place in the animal organism.

Vitamin B_1 occurs in nature as

1. the free compound.
2. the phosphoric acid ester (cocarboxylase).
3. the phosphorus-protein complex.
4. the monophosphate.

The relative amounts of these forms vary in different tissues:-

milk contains predominantly the free vitamin and vitamin-protein complex, (38).

in skeletal and heart muscle - the amount of free vitamin /

vitamin is greater than the phosphorylated compound,

in brain and liver - cocarboxylase and protein complex predominate, (39).

METABOLISM OF VITAMIN B_1

The vitamin is absorbed from the small bowel, and partly secreted in the gastric juice, possibly by diffusion. It is not stored to any appreciable extent in the organism: the amount actually present is sufficient to maintain health for only a few days. A daily intake of vitamin B_1 is therefore essential for normal functioning of the human body. The organism absorbs only enough of the vitamin to satisfy immediate needs, the excess is excreted forthwith or destroyed.

It is absorbed from the bowel in the free or the phosphorylated form. Phosphatase from the duodenum of pigs can evidently phosphorylate vitamin B_1 in vitro, (40).

According to Sinclair,(41), vitamin B_1 circulates in the blood plasma and cerebro-spinal fluid in the free form, where the concentration is found to be approximately 1γ per 100 c.c.

Constant phosphorylation and dephosphorylation take place inside all cells of the body.

It is stated that liver, kidney, muscle and brain can convert the vitamin into cocarboxylase. Nucleated blood /

blood cells and probably all nucleated cells of the animal body can phosphorylate vitamin B_1. It has been suggested by Goodhart and Sinclair, (42), that mammalian erythrocytes obtain their cocarboxylase while nucleated in the bone marrow.

In the early days of vitamin research, many theories were advanced to account for the mode of action of the "anti-neuritic factor". They may conveniently be tabulated as follows:-

Eijkman: that it "neutralised" a toxin in rice.

Schaumann: that it was concerned in phosphorus metabolism.

Vedder: that it acted as a nerve stimulant.

McCarrison: that it was a necessary constituent of the nucleus of the nerve cell.

Mebius: that it controlled water metabolism.

Hopkins: that it stimulated internal secretions.

Lumière: that it was required for stimulation of the digestive secretions.

Cuboni: that it had an enzyme-like action.

Many of these suggestions seem at first sight to be irreconcilable, nevertheless our recent studies have indicated that some of them, at any rate, are bound up in our modern interpretation of the mode of action of vitamin B_1.

Many years ago, Fraser and Stanton demonstrated that the human (and avian) nervous system could be deprived of vitamin B_1 with impunity, provided the diet contained no carbohydrate. Funk also suggested that carbohydrate /

carbohydrate metabolism and vitamin B_1 were somehow connected with one another.

It is curious that no further investigation of any importance in this connection, was carried out for some years.

Abderhalden, (43), however, in 1933 shewed that, in animals, deprivation of vitamin B_1 caused a rise in the blood sugar and glycogen content of the liver, and suggested that the vitamin plays a part in tissue oxidation. This was confirmed by Japanese investigators who demonstrated a low oxygen consumption by the liver tissue of B_1 - avitaminotic pigeons, and diminished oxygen capacity of the blood of a dog suffering from vitamin B_1 deficiency.

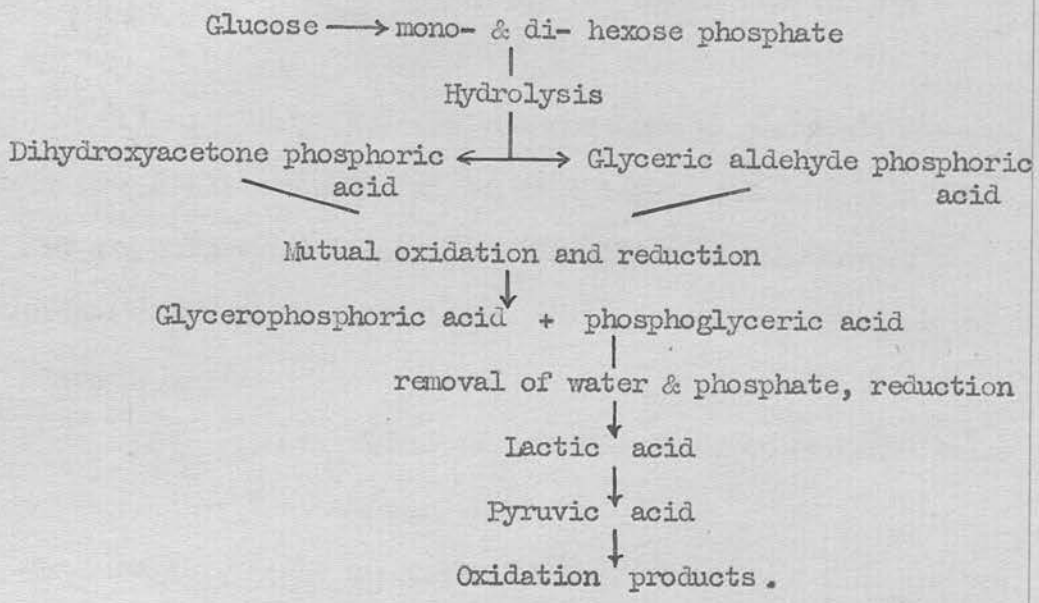
The work of Peters and his collaborators has helped considerably in the elucidation of the role vitamin B_1 plays in carbohydrate metabolism.

Kinnersley and Peters in 1929, (44), found an increase in the amount of lactic acid in the lower part of brains of pigeons subsisting on a vitamin B_1 deficient dietary.

A continuation of this work, (45), demonstrated that the minced brain of such avitaminotic birds, respiring in the presence of glucose and Ringer-phosphate solution, shewed a diminished oxygen consumption. The addition of vitamin B_1 produced a large increase in oxygen uptake. This came to be known as the "Catatorulin effect". The investigators concluded that "The localised character /

character of the chemical lesions proves that vitamin B_1 is associated with the intermediate metabolism of carbohydrates."

The steps in the oxidation of glucose in the human body are probably as follows:-



Enzyme activity enters into each step, and it is thought that vitamin B_1 in the form of its pyrophosphoric ester (cocarboxylase) acts as a specific catalyst in the degradation of pyruvic acid.

If this view is correct, vitamin B_1 deficiency should be associated with the accumulation of pyruvic acid in the blood. Now, being a ketonic acid, pyruvic acid combines with sodium bisulphite, though it must be observed that, as a test, it is not specific, (46). Thompson and Johnson, (47), found large amounts of bisulphite-binding substances in the blood of polyneuritic pigeons and rats which they considered largely to be pyruvic acid.

Similar /

Similar results were obtained in the blood, urine, and cerebro-spinal fluid of human beri-berics by Platt and Lu, (48).

Under normal physiological conditions, pyruvic acid is metabolised in a number of different ways, according to the type of cells in which the carbohydrate breakdown occurs.

It is believed that vitamin B_1 catalyses principally two closely allied reactions - the decarboxylation, and the carboxylation of pyruvic acid; while the former reaction prevails in yeast, the latter predominates in animal tissues.

It is, moreover, possible that the vitamin takes part in other reactions as well.

The Decarboxylation Reaction: In the anaerobic fermentation of carbohydrates, pyruvic acid is decarboxylated and yields acetaldehyde and carbon dioxide:

$$CH_3.CO.COOH \xrightarrow{\text{(vitamin } B_1 \text{ - pyrophosphate)}} CH_3.CHO + CO_2$$

Lohmann and Schuster, (49), shewed that the rate of carbon dioxide evolution is dependent on the concentration of "cocarboxylase" (vitamin B_1 pyrophosphate). That this reaction of yeast is not confined to pyruvic acid is indicated by the work of Long and Peters, (50), who shewed that alpha-oxo-carboxylic acids, such as keto-glutaric, keto-valeric, and keto-butyric acids are also decarboxylated by the enzyme system of yeast.

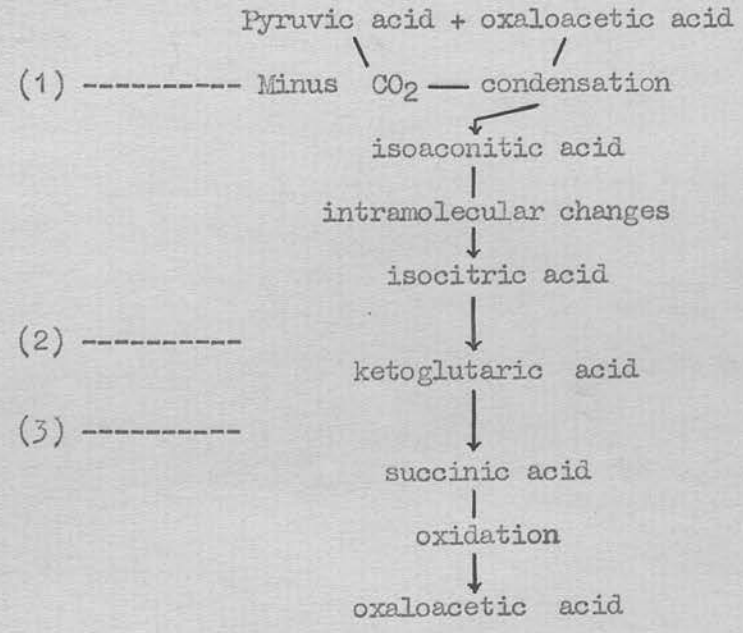
The Carboxylation Reaction: Wood and Werkman, (51), have indicated /

indicated that in animal tissues, in plants, moulds, and in certain bacteria, pyruvic acid is carboxylated and yields oxaloacetic acid:

$CO_2 + CH_3.CO.COOH \longrightarrow COOH.CH_2.CO.COOH$

The actual occurrence of this reaction has not yet been directly proved, but a considerable amount of evidence has accumulated in favour of this concept.

The most recent evidence suggests that the following steps take place in the degradation of pyruvic acid, (52).



The pyrophosphate of vitamin B_1 almost certainly plays a part in step (1), and possibly in steps (2), and (3) as well.

Walshe, /

Walshe, (53), has asked the question "Is pyruvic acid possibly the toxic metabolite, which I have postulated as the common direct poison in polyneuritis?" The answer to this question has, unfortunately, not yet been found. Peters, however, has cautioned against adopting this view without further verification. Injections of pyruvate so far, have failed to produce neuritic symptoms: nevertheless there is a considerable weight of opinion in favour of the hypothesis that incompletely oxidised metabolic products are directly responsible, and it is doubtful whether attempts to produce polyneuritis by the injection of a known intermediate of carbohydrate metabolism have really been exhaustive.

The action of vitamin B_1 in carbohydrate metabolism has been discussed only in its relation to the utilisation of pyruvic acid. This would seem to be the most important action; however, other observations may also be mentioned in connection with disturbed carbohydrate metabolism in vitamin B_1 deficiency.

1. There is convincing evidence of an upset in glycogen storage and blood sugar levels in B_1 avitaminosis; there is no unanimity of opinion, however, on the actual effect of vitamin B_1 on the blood sugar level. Japanese workers have reported a rise of blood sugar, and failure to deposit liver glycogen in cases of thiamin-deficiency. There must /

must, nevertheless, be a species difference as Lewinson, (54), has demonstrated an initial fall in blood sugar, and later a rise in dogs suffering from avitaminosis B_1, whereas in pigeons, hyperglycaemia occurs throughout. De Lucia and Morelli, (55), in 1938 observed that injections of 1 mgm. of thiamin caused a slight fall in the blood sugar values of normal persons. Wilson, (56), in 1939, however, stated that injections of 10 mgms. vitamin B_1 intravenously, have no effect on the fasting blood value. Apart from species differences, marked irregularities in experimental evidence appear to be complicated by attendant inanition or subsidiary deficiencies.

2. There is no doubt that a diet rich in carbohydrate brings on the symptoms of polyneuritis more rapidly than a diet containing much fat: Westenbrink, (57), has observed that pigeons on a high carbohydrate diet, devoid of fat, have shewn polyneuritic symptoms in 19 days, whereas such symptoms only appeared after 27 days in birds fed on a high fat diet which contained no carbohydrate food. This work has since been confirmed by other investigators. Richter, (58), in his interesting research on "free choice" experiments has added further evidence, by demonstrating that rats on an adequate self-selection, though thiamin-deficient diet, have had a craving for fat, and aversion to carbohydrate and protein, at the height of their deficiency.

3. Findlay, (59), in 1921 found that the livers of pigeons suffering from beri-beri were deficient in glyoxalase. /

glyoxalase. Ten years later, Vogt-Moller, (60), described vitamin B_1 deficiency as "an intoxication with methyl glyoxal, which results from a shortage of the co-enzyme for glyoxalase". Since then, methyl glyoxal has been found in the urine of polyneuritic experimental animals, and more recently, in the blood and urine of cases of beri-beri, (48).

4. Fat metabolism is influenced by vitamin B_1 only in so far as the synthesis of fat from carbohydrate is concerned. The utilisation of ingested fats apparently does not require the presence of the vitamin, (61).

5. Water metabolism is connected in some way with the action of vitamin B_1, probably through the metabolism of carbohydrates.

Further observations on the action of vitamin B_1:

6. Thiamin also plays a part in the regulation of the nervous system. During nerve excitement, acetyl choline and vitamin B_1 are liberated from the nerve. Thiamin, itself, cannot bring about contractions of the gut, though acetylated vitamin B_1 has the power to do so.

7. Cowgill and others, (62), have shewn that an increase in the secretion of thyroxin necessitates an increased amount of the vitamin. This is bound up with carbohydrate metabolism. A similar relationship has been demonstrated for vitamin B_1 and insulin, (63).

8. There is also a close relationship between vitamin B_1 and another hormone - that of the suprarenal cortex. /

cortex. In B_1 - avitaminosis, hypertrophy of the adrenal cortex occurs: this may be cured by the administration of vitamin B_1.

9. Sarda, (64) has reported that sex hormones and vitamin D, - substances which belong to the cyclo-pentano-perhydro-phenanthrene type - delay the onset of vitamin B_1 deficiency.

10. Research so far, has only touched the fringes of the relationship between B_1 and the other vitamins. All that is known up to the present, is that vitamin A appears to act antagonistically, since increase of vitamin-A intake aggravates the symptoms of B_1 deficiency.

11. Recently, (65), (66), it has been shewn that there is some connection between vitamin B_1 and both zinc and manganese metabolism.

Further actions, no doubt, will be revealed in the future. Not the least interesting outcome of further research will be the correlation of chemical pathology with the symptomatology of beri-beri.

At the present time, it is believed, (67), that the essential mechanism of vitamin B_1 action is due to "the ability of the vitamin to undergo reversible oxidation-reactions with the intermediary formation of a disulfide. It is also known that.....the vitamin action is due to the specific structure of the entire molecule."

MORBID ANATOMY OF BERI-BERI.

In discussing the pathology of beri-beri it is at once important to realise that from this aspect the condition resolves itself into two categories:

Firstly: the chronic polyneuritic in which the pathological nervous changes are constant; it is interesting also to note that they are constant whether the person died from beri-beri or whether a state of B_1 deficiency occurred, associated with such diverse conditions as chronic alcoholism, pellagra, sprue, colitis, pernicious anaemia, or diabetes. There is general tendency to regard the polyneuritis arising from a thiamin deficiency as beri-beri even if another disease condition is present.

Secondly: the acute "fulminating" cardiac type, in which there is often plenty of fat, and but little degeneration of nervous tissue. The principal post-mortem changes are in the heart.

It is stated, (20), that "the chronic cases" (of beri-beri) "seldom die from beri-beri itself, but from complications, such as tuberculosis, typhoid, or some other infection." This may well be; nevertheless, one must go further. In my practice in the Far East, it was not infrequently found that, a Chinese or a Malay who was suffering from a severe illness, began to shew signs of developing beri-beri during the course of that illness. The reason for this of course is obvious: the native population to a great extent subsists on a border line diet, and the onset of a severe infection is sufficient to tip the balance, in /

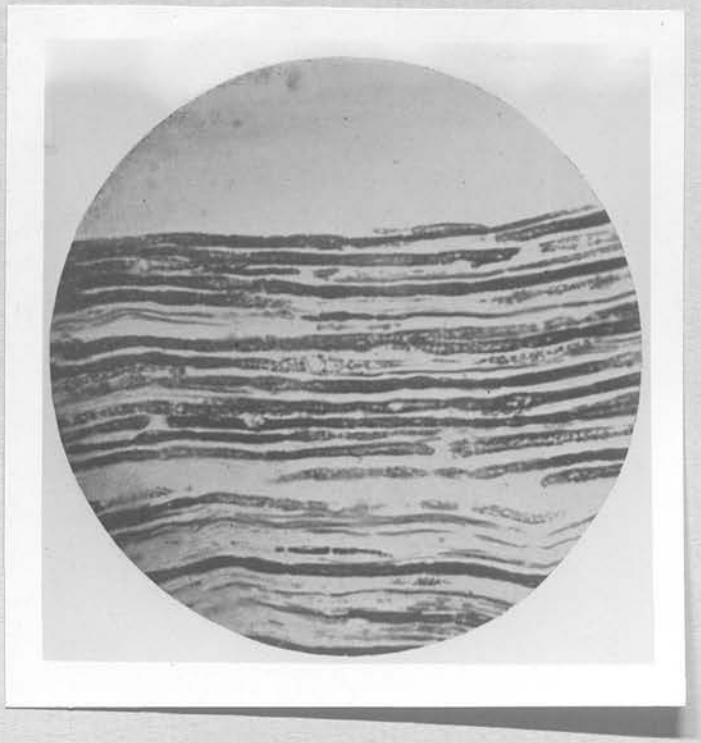
in virtue of the fact that illness increases the need for vitamin B_1. In the East one has always to be on guard against the onset of beri-beri affecting the indigenous races, and to institute specific therapy in time.

Mortality from "tuberculosis, typhoid or some other infection" will be considerably reduced in "endemic" areas of beri-beri, once this fact is fully realised. I am perfectly certain that not a few of these cases die as a result of heart failure induced by a depletion of the body's store of vitamin B_1 occasioned through poor diet and the infection itself.

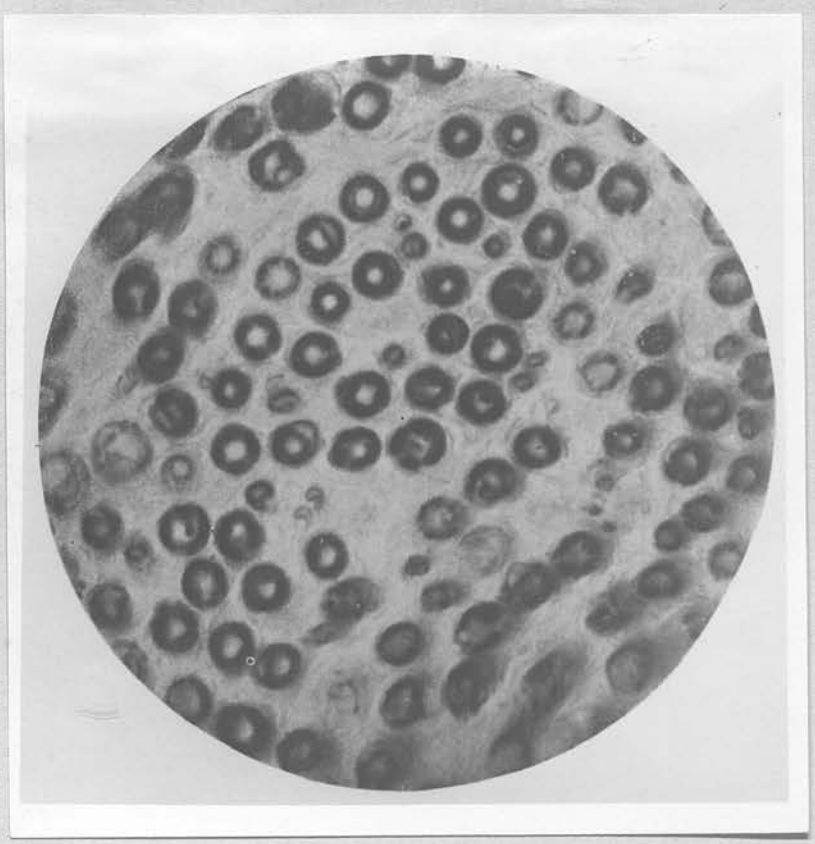
It must be admitted that pathologists often are unable to determine whether death has been due to beri-beri, sprue, pellagra, chronic alcoholism or some other closely related condition; hence any classification of deficiency diseases from the standpoint of pathology cannot be satisfactory. Nevertheless despite our limited knowledge of the fundamental pathology of beri-beri, the clinical findings can in most cases be correlated with the condition at autopsy.

The most characteristic lesion is a multiple neuritis, this occurring in varying degrees of severity; other changes are to be found mainly in the heart and musculature, - oedema and anaemia often being found as well.

NERVOUS SYSTEM AND MUSCULATURE: As one would expect, the pathological distribution of the nervous lesions conforms to the condition found clinically. Just as symptoms are initially /



Longitudinal section of popliteal nerve from a case of "dry" beri-beri, shewing different degrees of degeneration of the medullary sheath. (Weigert-Pal stain).



Cross section of popliteal nerve from a case of "dry" beri-beri, also shewing degeneration of the medullary sheath. (Weigert-Pal stain).

initially most often referred to the feet and legs, so does it occur that the nerves to the lower extremities are implicated early and are most commonly affected.

It is often remarked that only seldom are the cranial nerves above the 7th involved. This statement requires comment. Firstly it is unusual to find clinical evidence of any involvement of the cranial nerves unless in very severe cases; secondly, however, autopsies carried out on patients who have died as the result of chronic beri-beri seldom fail to demonstrate degeneration in most of the cranial nerves, most noticeably affecting the vagus. This was shewn many years ago by Scheube, Hamilton Wright and others.

Macroscopically the peripheral nerves appear to be normal: histological examination, however, reveals that the distal portions of the nerves are most seriously altered. The pathology is characterised by an early pan-neuritis which commences as a vacuolar degeneration of the cells of Schwann. The axis cylinders later shew fragmentation or atrophic changes and Wallerian degeneration may be demonstrated.

Clinical signs of neuritis in thiamin-deficient states may evidently occur, however, without any obvious change in the myelin sheath, (68).

The sciatic nerve is most commonly affected, and in the average case, early degeneration occurs in /

in the brachial, more or less at the same time that late changes are observed in the former.

The sympathetic nerve plexuses, cardiac, coeliac and splanchnic, are also frequently involved.

Recent work on the nerve changes shews that regeneration and degeneration occur side by side.

In "dry" beri-beri, the muscles supplied by the affected nerves are atrophied, especially in the legs, arms and diaphragm. The changes are simply those which occur in any polyneuritis - cloudy swelling, fatty degeneration, loss of cross striation, and atrophic sarcoplasm.

In the "wet" type, there is also oedema and separation of the muscle fibres.

Many years ago, (69), Bentley described congestion and softening of the brain, cord and meninges. According to Vedder, (31), also, there is not infrequently, in all tracts of the cord, changes similar to those found in the peripheral nerves. Degenerative changes have been found in the anterior and posterior nerve cells, as well as in the sympathetic ganglia. Vedder therefore concludes that beri-beri is not a simple neuritis, but a degeneration of the entire nervous system.

These findings are extremely interesting in the light of recent descriptions of the Encephalopathy first reported by Wernicke in 1881.

Of Campbell and Biggert's, (70), twelve cases, only one was considered to have been addicted to alcohol, which /

which, in the past, has been held responsible as the causative factor in the disease. The other cases all shewed one common factor - vitamin B_1 deficiency.

Confirmation of the view that thiamin deficiency is the principal causative factor of the disease comes from Wortis' observations, (71), that patients with the Wernicke syndrome are unable to metabolise pyruvic acid normally.

THE HEART:

Cardiac failure is the cause of death in acute fulminating "shôshin" and is also found in chronic cases dying from a sudden increased need for the vitamin which is not forthcoming.

In this group, the classical feature at autopsy is a heart which is grossly enlarged and may be hypertrophied. This dilatation affects most noticeably the right auricle and ventricle; the former is most conspicuous as the blood contained in it may actually be seen through the paper-thin wall. Other organs of the body shew passive congestion most marked in the liver, and pulmonary oedema occurs in more than half the cases. Petechiae are found beneath the pleura, in the stomach and duodenum, while the vessels are hyperaemic. Almost fifty years ago, Ellis, (72), in a study of more than a hundred cases of beri-beri found the average weight of the heart to be 427.8 grams (normal = 288 grams). This was confirmed by Japanese workers in 1936.

The conus arteriosus is so markedly dilated, especially at the origin of the pulmonary artery, that Wenckebach /

Section of Myocardium from a case of

"wet" beri-beri, shewing advanced fragmentation.

Section of Myocardium from a case of "wet" beri-beri, shewing loss of striation, vacuolation and granular degeneration. (haematoxylin - eosin stain).

Wenckebach considers this fact to be of diagnostic value.

Cardiac enlargement has been measured radiologically by Kobayashi who considers this also to be of use in the diagnosis of beri-beri. To be perfectly frank, I consider such "niceties" to be a waste of effort. One who cannot diagnose beri-beri clinically as it occurs in the East has no right to turn to x-rays for assistance.

The heart muscle shews hydropic degeneration, and fatty change in the bundle of His' has been demonstrated by Shimazono. There is also an increase of intra- and inter-cellular fluid in some cases.

Post-mortem studies of beri-beri however, have contributed little towards an understanding of the pathogenesis of the disease. The criteria for diagnosis at autopsy are entirely unsatisfactory - they consist of

1) degeneration of the peripheral nerves,
2) absence of any other cause of death,
3) oedema,

and in "shôshin" -

4) dilatation of the right side of the heart, without evidence of organic cause.

Vitamin B_1 deficiency as it affects the Nervous System.

Engel and Phillips, (73), in 1938 administered beta -carotene or Ol. percomorph and riboflavin to vitamin B_1 deficient chicks and found that the nervous system was not affected. /

affected. As a result, they concluded that the nervous degeneration which occurs in human beri-beri is due to lack of dietary factors other than thiamin.

They consider that the striking response to vitamin B_1 is due to improved appetite and assimilation, and is not specifically related to nerve lesions. The rapidity, however, with which symptoms respond to therapy, I maintain, certainly cannot be accounted for solely by an improved appetite and assimilation. It seems more probable that the view held by Elvehjem, (74), is correct; he believes that the cause is a general disturbance of the carbohydrate metabolism.

As a result of my own observations, the pain and hyperaesthesia of beri-beri often disappears with adequate therapy in as short a time as 24 hours. Thereafter it may take weeks for a patient to regain the normal use of his legs, though it must be mentioned that if larger doses of thiamin are employed than is usual, full power in the limbs is regained the more quickly.

It would seem to be more or less definite that the initial recovery is due to a return of the function of the nerve cells, and that the subsequent progress which is so often slow, can be attributed to the somewhat lengthy process of remyelinisation of the nerve fibres.

I am of the impression that this recovery

is /

is hastened by giving the patient a diet not only with high content of vitamin B_1 but also containing excess of the other food factors.

Vitamin B_1 deficiency and cardiovascular failure.

The theory held by Scheube, Hamilton Wright and others in the opening years of the present century as to the cause of cardiovascular failure in beri-beri was that degeneration of the vagus nerve seemed to be the main factor.

Recently however, doubt has been cast on this belief, as the result of finding cases of "shôshin", which shewed but slight signs of degeneration of the vagus.

Aalsmeer and Wenckebach, (75), in 1929 described their water retention or oedema hypothesis. They stated that lack of vitamin B_1 produces a metabolic disturbance which in turn, causes skeletal and cardiac muscles alike to absorb water. This theory does not appear to be far from the mark in that excess fluid has been demonstrated within and between cardiac cells. Moreover, there is no doubt that heart failure is much more common in beri-berics of the "wet" type, and again, the exhibition of thiamin to "shôshin" is dramatic in the extreme.

Weiss and Wilkins, (76), in their notable work indicated that not only the heart but also the peripheral circulation may be at fault in the mechanism of the circulatory disorders of beri-beri. Lesions of the sympathetic nerves too, may possibly play a part in the causation /

causation of the peripheral vascular phenomena.

The conclusions they reached are most instructive and no modern work on beri-beri would be complete without a reference to their summary:-

"1. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in the United States. This report is based on a study of 120 such cases, 35 of which were investigated within 2 years.

2. The cardiovascular manifestations depend on changes in the nervous system, in the vascular system, and in the myocardium.

3. Tachycardia followed by bradycardia, gallop rhythm, vagal reflex irritability, dilatation of the heart, dyspnoea, orthopnoea, and pulmonary congestion, associated with bounding arterial pulsations, arterial "pistol sounds", engorged veins, warm skin and oedema are the usual clinical features of severe cases.

4. The haemodynamics are characterised by low vital capacity of the lungs, high venous pressure, and by a relatively or absolutely increased velocity of blood flow and decreased peripheral utilisation of arterial oxygen. The osmotic pressure of the blood is usually moderately low and frequently remains essentially unchanged while the oedema disappears.

5. The electrocardiograms were normal in 7% of 67 cases. The main abnormalities consisted in changes in the T waves and prolongation of the electrical systole (Q-T).

The electrocardiographic changes in pellagra or beri-beri probably are due to the B_1 component of the vitamin deficiency.

6. The myocardium often showed "hydropic" degeneration of the muscle and conductive fibers and increase in the intercellular substances, but unaltered water content.

7. The cardiovascular disturbances caused by nutritional deficiencies do not form a rigid clinical syndrome. Right ventricular failure, left ventricular failure, arteriolar dilatation and increased blood flow, peripheral circulatory collapse and shock singly, or in combination, have been observed.

8. The onset of the disease may be sudden or gradual. Patients with the severe form of the disease show a tendency to fever, to bronchopneumonia, and to fatal circulatory collapse. Under therapeutic measures such as rest, cardiac drugs, diets rich in vitamin B_1 or crystalline B_1, all the cardiovascular disturbances usually revert to normal.

9. The clinical symptoms and signs, the blood chemistry, the myocardial changes, the haemodynamics and therapeutic responses correspond to those described in "Beri-Beri heart" in the Orient. The disease as observed in Boston, however, is characterised by more varied and more generalised involvement of the cardio-vascular system.

10. Evidence is presented indicating that vitamin B_1 deficiency plays a primary role in the precipitation of the disease. Alcohol also is a significant factor, not only because /

because it supplies calories without vitamin B_1 but also because its metabolic effect is similar to that of a pure carbohydrate.

11. The rate of response to vitamin B_1 in "alcoholic" and "non alcoholic" beri-beri varies. The arteriolar system shews a more rapid change than the heart. The cardio-vascular disorder usually disappears before the polyneuritis. The factors influencing therapeutic responses are discussed.

12. In normal subjects, as well as in patients with diseases other than vitamin B_1 deficiency, even large doses of crystalline B_1 produce no appreciable effects.

13. The condition here described bears pertinently on the clinical behaviour and the mortality rates of alcoholic and non-alcoholic patients with vitamin B deficiencies (beri-beri and pellagra).

It may explain the poor reaction of these patients to increase in metabolic rate, such as occur in febrile infections, in hyperthyroidism, or under surgical operations. The therapeutic indications under these conditions are discussed."

It has been suggested that the accumulation in the heart muscle, of pyruvic acid or methyl glyoxal, may be productive of the cardiac manifestations of beri-beri. Research, however so far, has failed to produce signs of heart failure, following injection of these metabolites, (77).

It is important to remember that physical exercise plays a crucial role in the production of the varied manifestations of the disease. Polyneuritis may predominate

and /

and therefore cause invaliding early: rest protects the myocardium. If the patient is not disabled as a result of the neuritic involvement and performs severe manual labour, heart failure is a common phenomenon and he works until he drops, - both literally and metaphorically.

The mechanism of oedema.

Definite proof as to the cause of oedema in beri-beri has not yet been discovered. Many have been the views put forward: that it is due to a lowering of colloidal osmotic pressure, damage to the capillary walls, interference with the lymphatics or connected with salt retention, high fluid intake, warm environment or disturbed innervation.

At the moment the hydrostatic theory of Meyers, (78), would seem to have more followers than any other.

We now know that no apparent renal changes occur along with the oedema, and Meyers is of the belief that it is due to a lowering in tone of the arterial walls, accompanied by an increased tension in the capillaries.

The rapid blood flow, warm extremities, flushed colour and increased pulse pressure, all lend weight to this conception.

For some time, however, I have felt that the oedema of beri-beri occurs as the result of some accessory deficiency superimposed on lack of vitamin B_1.

It is interesting to note that in favour

of /

of this new hypothesis, vitamin B_6 -avitaminosis in rats produces, over and above dermatitis, oedema, (79).

May the oedema of "wet beri-beri" be due to lack of pyridoxin (vitamin B_6)?

I consider this to be a very probable explanation. If the factor is not pyridoxin, I feel certain that the oedema is due to lack of some other component of the vitamin B_2 - complex, hitherto undifferentiated.

The gastro-intestinal tract and vitamin B_1 deficiency.

It is now quite definite that vitamin B_1 is essential for the normal functioning of the gastro-intestinal tract. It is not nevertheless certain how this deficiency acts.

Many years ago, McCarrison, (80), stated that lack of vitamin B_1 caused degeneration of Auerbach's plexus, this resulting in an upset of the alimentary tract.

There is associated also atrophy of the glandular elements of the stomach and intestine.

Rowlands and Browning, (81), in 1928 described a loss of tone as the result of vitamin B deficiency: many authorities now believe that this is specifically due to loss of the B_1 component, though B_6 is probably also implicated.

Sparks and Collins, (82), consider too that there is loss of tone. On the other hand, such an eminent authority on gastro-intestinal movements as Alvarez, (83), has been unable to demonstrate any gastric changes due to /

to lack of vitamin B_1. It is only just, however, to remark that the latter observations were the result of experimentation on one volunteer, deprived of vitamin B_1 for only six weeks.

Webster and Armour, (84), have shewn that secretion of gastric juice is impaired, and it is interesting to note that very recently Von Papp has demonstrated the secretion of acid in the stomach, only half an hour after injection of vitamin B_1, even in normal individuals.

Multitudinous have been the recent studies on vitamin B deficiency and the gastro-intestinal tract. Many of the observations recorded, however, are difficult to evaluate accurately, inasmuch as, in many of the cases mentioned, there have been concomitant deficiencies of other factors.

All that we can say at the moment is that beri-beri patients almost invariably describe gastro-intestinal symptoms and it is likely that these are due to lack of vitamin B_1, or to an associated deficiency of other factors in the B-complex.

Vitamin B_1 deficiency in relationship to growth.

Osborne and Mendel, (85), in 1913 found that protein-free milk contained a substance necessary for normal growth in rats, and concluded that it was identical with the antineuritic factor.

It is now known that vitamin B_1 is essential for normal growth in the young and for maintenance of /

of normal weight and health in the adult.

Is it possible that subsistence on a vitamin B_1 deficient diet throughout the ages may have something to do with the fact that so many of the races in the Far East where beri-beri is "endemic", are of short stature?

Investigation in America has shewn that increase in the vitamin B_1 content of the diet, has been followed in most cases by an improvement in growth, appetite and body weight.

It is believed that there is a close relationship between the vitamins, other essential substances contained in food, and the active principles derived from the glands of internal secretion. These substances, if adequate and in balance, form a suitable environment for all cells of the body. If however, there is an imbalance, the cells must suffer and disease result. We are now aware that vitamin B_1 influences cell metabolism, - nay more, it is essential for normal, healthy, cell metabolism, - and its absence results not only in degeneration of the peripheral nerves, not only in cardiac failure or oedema, but also in cellular alteration in the stomach, intestines, the pancreas and liver, the suprarenals and gonads, and probably in most, if not <u>all</u> of the tissues of the human frame.

CLINICAL SIGNS AND SYMPTOMS.

A small Indian baby, two months old, lay dying cradled in the arms of his weeping mother, who, herself, was unable to walk. This picture was my introduction to beri-beri - striking in intensity, stark in reality, and dramatic in tragedy.

From then on, the condition occurred every now and then in my practice until June, 1941 when it broke out in full fury, amongst the Malay and Chinese ratings of the auxiliary vessels at Singapore.

Forty-seven of these men developed frank beri-beri, others shewed signs definitely attributable to vitamin B_1 deficiency, or demonstrated manifestations of avitaminosis generally.

Many of my remarks are taken from observations on this "outbreak".

It is interesting to note that one of these forty-seven cases, has a Japanese plane to his credit and another probable.

As a result of this epidemic of beri-beri I was allowed to institute an entire reform of the diet issued to the crews in our ships.

At the outbreak of the war with Japan, the health of our sailors was extremely good, indeed it had probably never been better and I should here like to pay a tribute /

tribute to these men; Malaya had not experienced any of the hardships of war for more than a century, and the ratings under my care and attention stood up magnificently to the incessant attacks from the air.

Anyone looking through the literature cannot fail to observe that in the past most attempts to classify beri-beri have been based on its most gross manifestations: at the present time, the pendulum has swung so far, that the signs and symptoms of the "mother condition" to a great extent have been lost sight of in the plethora of complaints attributed to thiamin deficiency.

The condition of frank beri-beri as met with in the East, is practically unknown in England. Yudkin in 1938 having observed a case - an Indian who had come to this country from Calcutta - made a search of the literature and failed to find a single reference to true beri-beri reported in England, (86). Despite the fact that the classical disease does not occur here, interest to a certain extent has been maintained, inasmuch as it is recognised that study and researches on beri-beri have led to most of the later work in connection with the entire group of the avitaminoses, also in that evidence is accumulating rapidly that certain forms of the condition are common in this country.

From a fairly wide experience of the condition, I find that most doctors, who are in contact with the disease refer to beri-beri as occurring in the following manner:- /

manner:-

1. "dry" beri-beri.

2. "wet".

3. acute cardiac, or shôshin.

4. infantile

and we may add

5. subacute.

I suggest that the above classification is sensible, simple, yet comprehensive.

It must be remembered, of course, that one group may merge into another, and that there may be a great variety in degree and combination of symptoms.

Eddy and Dalldorf, (87), have stated that "It is customary to consider the nervous signs of beri-beri the first to appear. This is probably not true. Significantly Shimazono, (32), in characterizing the disease, lists the three major features in the following order: cardiovascular symptoms, oedema and neuritis.

The usual sequence is mild cardiac symptoms with slight oedema and dyspepsia, followed by nervous symptoms."

I entirely disagree with both of these views. Beri-Beri, as it occurred in Singapore, commenced - excepting the pernicious cardiac group - with dyspepsia: "sahaya ta'boleh makan, Tuan" (I can't eat, Sir) or "ada sakit perut, Tuan" (I have pain in my stomach, Sir) were almost always the first complaints. The next most common symptom was "pins and /

and needles" in the fingers or toes - then followed poly-neuritis, oedema and cardiovascular symptomatology, in that order.

Probably the most important group is that of the early cases: if treatment is carried out in the initial stages, the more severe manifestations do not appear.

The signs and symptoms of the ordinary developing case of beri-beri are almost identical with those of the patient who gives evidence of having lived for some time in a partly deficient state and they will be dealt with together under the group termed

SUBACUTE BERI-BERI.

Scheube in 1900 referred to this type as Rudimentary Beri-Beri.

As in these days, loss of appetite is always complained of: it is probably the result firstly of lack of tone in the musculature of the stomach, and secondly of constipation which is also so common.

There is, in addition, a vague epigastric discomfort, a feeling of oppression in the stomach which may even amount to an actual dull pain.

At the same time, the patient may state that he has numbness, or "pins and needles" in his fingertips and toes, - indeed this may be the only complaint. Another may report because of tiredness and weakness, that he is unable to do his work, and that on going up hills or if engaged in any task entailing exertion, he feels breathless and has palpitation. /

palpitation.

Tachycardia, in my experience, however, has been significant by its absence.

Hawes, who until recently was Professor of Medicine in Singapore, and who was the first to treat the acute cardiac emergency of Shôshin effectively, in a personal communication, stated that

"Beri-Beri as we saw it in Malaya, affecting heavy rice-eaters, is very different from experimental beri-beri in human beings on a more balanced diet. There is so much nonsense in this country about vitamin B_1 that tachycardia is often diagnosed as beri-beri, although as far as I can remember, I never saw a true tachycardia due to B_1 deficiency."

On the other hand, some patients have complained of anginal sensations - praecordial pain on exertion - and this has disappeared on exhibition of thiamin.

In the course of my present naval duties, cases occur every now and then of "Effort Syndrome". They are being treated with B_1 - both orally and by injection: results are so far encouraging but are not yet sufficiently comprehensive for any conclusions to be reached.

Irritability and depression were frequently complained of during the outbreak of beri-beri in the ships - they were encountered too often to be accounted for by coincidence.

It is interesting also that many cases of Tropical Neurasthenia, as affecting the European population of /

of Singapore, whether accompanied by alcoholism or not, were found to derive great benefit as the result of treatment by vitamin B_1. I well remember one man of 47 years of age who for some time had complained of "a band around the head", headaches, backache, and other symptoms which in the absence of any pathology, led one to diagnose neurasthenia with confidence.

Prior to the administration of B_1, he had been treated with "tonic nerve sedatives", without any improvement.

As the result of vitamin therapy he stated that all his complaints had vanished and that he had never felt better in his life.

Williams believes that there is a strong parallel between vitamin B_1 deficiency and neurasthenia, as does Wilson, (88), who goes so far as to state that such feelings as "band around the head" are definite manifestations of B_1 deficiency. Certain it is, that many cases of tropical neurasthenia do benefit from treatment with this vitamin.

In the literature, fever is often mentioned "as an early symptom of beri-beri". Beri-Beri is however, <u>not</u> a febrile illness. A rise in temperature is observed every now and then but it has always been due to some intercurrent infection such as common cold, diarrhoea and so on.

Scheube stated that the early fever was often /

often accompanied by catarrhal symptoms. Pyrexia, however, is never the result of beri-beri, or characteristic of it.

Apart from the "pins and needles" sensation there are other initial sensory disturbances.

Chief and most constant among these is anaesthesia. When examining any new recruit for the S.S.R.N.V.R., when I tested the 2,500 ratings for beri-beri, or if at any time I suspected the condition, one of my first investigations consisted in running a pin over the tibiae. Anaesthesia over the lower third of the shin bone is a surprisingly regular manifestation of early beri-beri, and the finding thereof is of the utmost importance. This loss of sensation is initially only diminished to a slight degree; it is however, definite. No other area of the body is so affected at this stage of the disease.

Scheube and recently Jolliffe, (89), have described hyperaesthesia of the shin. I cannot substantiate these findings: on the other hand, hyperaesthesia of the underlying muscles is absolutely constant. The pain is generally described as dull and aching and is always accentuated even by the slightest pressure. The patient therefore resents and instinctively avoids having his limbs handled. In the early beri-beric, only the muscles of the calf are thus affected. I have the impression that these sensory disturbances are worse on cold, rainy days. They are always bilateral.

Other early manifestations are stiffness and weakness of /

A typical case of "dry" beri-beri, shewing advanced atrophy of leg muscles and foot drop.

of the legs, and as a result, indisposition to walk far.

Oedema of the feet and ankles I consider to be not only a complaint of the developed "wet" beri-beri but also commonly of the subacute phase. This oedema may be difficult to demonstrate but will not be missed, if the examiner using the index finger of his right hand, presses for one minute, one inch above the internal malleolus.

The occurrence of oedema as an early sign will also be referred to later.

The patient may demonstrate the above symptoms either in the opening stage of beri-beri, or may continue in this condition for months or even years, in the absence of specific therapy, with periods of slight improvement alternating with exacerbation of the symptoms, but without material change.

Should the disease progress, the patient will then be referred to, as suffering from either "dry" beri-beri, or "wet" beri-beri, depending on whether or not oedema occurs: in the latter group, anasarca predominates to such an extent that beri-beri has always been subdivided into these two groups, and will continue to be thus differentiated until the condition no longer exists.

DRY BERI-BERI.

Two recent works, (20), (34), which deal extensively with vitamin B_1 deficiency state that beri-beri is an ascending peripheral neuritis. This conception I believe to be misleading. It is true that involvement of the /

the nervous system can be demonstrated as occurring in the legs usually before it is manifest in the arms; I have however, observed numerous cases where both motor and sensory changes appeared in the hands and wrists, more or less at the same time as the lower limbs were affected. Where this occurred it was noticed that the patients all had to use their hands extensively in connection with their work. It would therefore seem that nerves and muscles which are being used to the greatest amount are first involved, and that beri-beri is essentially not an ascending polyneuritis. This at once differentiates the condition from Landry's paralysis.

When resident in the Royal Sick Childrens' Hospital, Edinburgh in 1936, I well remember a case which was diagnosed as Landry's paralysis. The manner in which the paralysis ascended and later receded bears no likeness to any case of beri-beri I have ever seen.

The major clinical manifestation of dry beri-beri is a symmetrical peripheral neuritis.

Sensory disturbances:

Paraesthesia is very common, and occurs in many different forms. Some patients complain of "pins and needles" or numbness, while others describe formication or even itching.

During the "epidemic" of beri-beri, three cases reported, complaining of a burning sensation in the soles of the feet. This condition is evidently not uncommon in /

in Somaliland and has previously been observed in Malaya: it is occasioned through deficiency, is connected in some way with beri-beri, and is certainly curable by administration of thiamin. Like other symptoms, these paraesthesias are increased on wet or cold days.

Hyperaethesia of the calf muscles is well marked in the dry beri-beric: in severe cases, the muscles of the forearm and the abdomen are also affected.

We have seen how, even in the subacute phase, an area of anaesthesia can often be found over both tibiae. This area may be more or less sharply circumscribed or be rather vague. It may spread over the dorsum of the feet, and up the inner surface of the legs.

The arms tend to be affected later, the fingers and extensor aspects of the forearm being the first to lose their sensitiveness.

It is stated that the trunk, neck and face may be attacked, and observers in Japan describe a circle of anaesthesia around the mouth.

Perception of heat, cold and painful stimulation are all diminished or lost in these anaesthetic areas: vibration and position sense is also deficient.

Motor disturbances:

These appear to be mainly caused by degeneration and paralysis of the muscles as a result of the neuritic involvement.

A predilection is shewn for certain muscles, the /

the extensors of the foot, and those muscles also supplied by the anterior tibial and peroneal nerves are usually the first to suffer, followed by the calf muscles, the extensors of the leg and later the glutei.

The arms are affected in a similar order, the extensors of the hand being implicated first.

Finally in severe cases, the abdominal muscles, the intercostals, diaphragm, and muscles of the larynx may also be involved.

The paralysis of muscles is accompanied by rapid and extensive wasting: fibrillary tremors are also commonly seen.

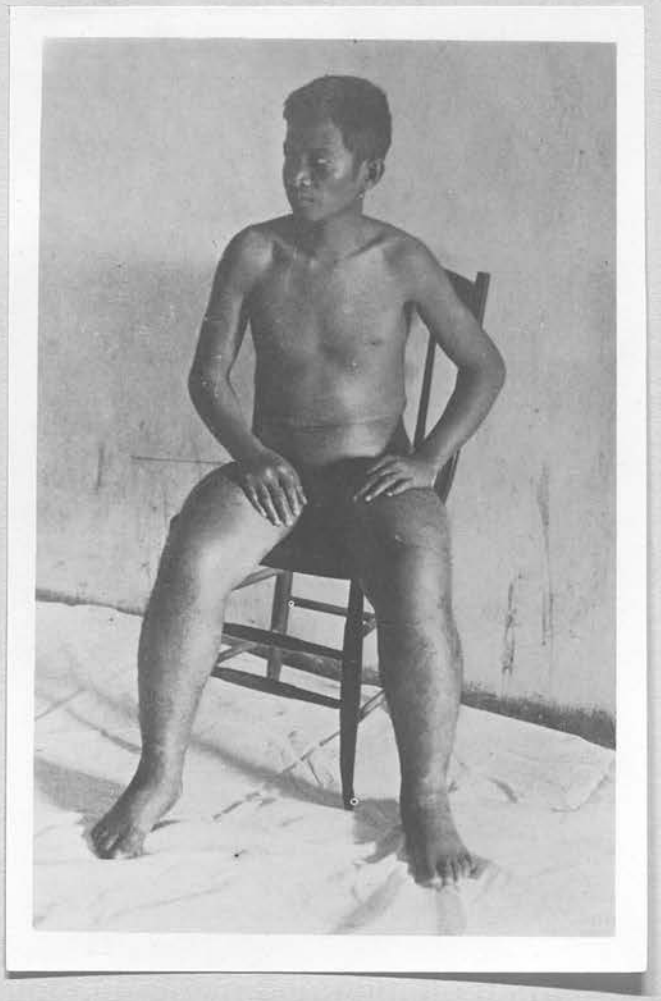
It is interesting to note that the sphincters are never affected.

Reflexes: Relatively early in the disease, the ankle jerk is lost: this is of importance diagnostically. The knee jerk in all cases which we call dry beri-beri, is always lost as well.

Curiously enough, I have observed two cases, where the knee jerk was completely absent in one leg, while it was either normal or only slightly diminished in the other.

It is said that in the very early stages, the knee reflexes may be exaggerated: none of my cases shewed any exaggeration whatsoever.

The beri-beri gait is almost characteristic: it has been compared somewhat fancifully to the walk of a person emerging from the water with wet clothes on, or walking in stiff /



A marked case of "wet" beri-beri,

shewing great oedema of legs and feet.

stiff clay.

In the mild form where the extensors of the foot are alone affected, the resultant effort to raise the foot sufficiently high, and to slap it down in order to avoid scraping the ground with the toe, attracts attention immediately. In the more severe cases, walking appears to be extremely difficult, the patient may require the assistance of another man's support, or the use of a stick, and his manner of progression is merely a shuffle.

True Ataxia and Rombergism were observed in two cases, but are not common manifestations of the disease. Many patients appear ataxic but this is chiefly caused by muscular weakness and not by inco-ordination.

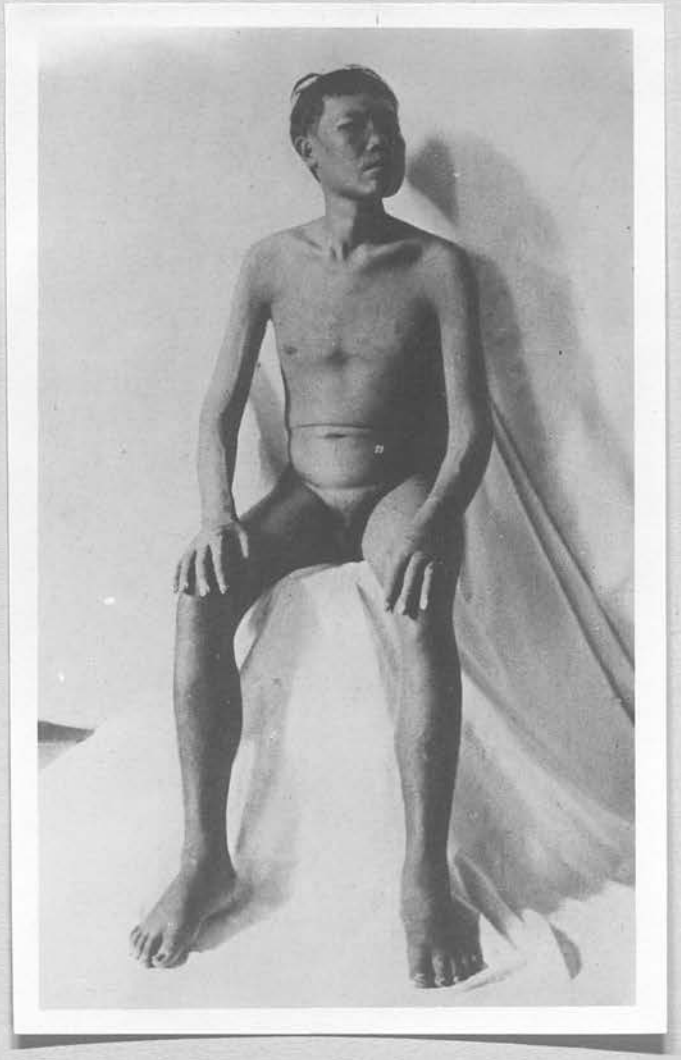
Cardiac upset is very common; this will be considered at the end of the following section, as it occurs more often in oedematous cases.

WET BERI-BERI.

Of the forty-seven cases of frank beri-beri affecting the S.S.R.N.V.R. ratings, only few shewed oedema.

In those cases which were relatively mild, the oedema affected only the dorsum of the feet and ankles: in patients more severely affected, the swelling occurred also higher up the legs, in the hands, and caused puffiness of the face.

Schretzenmayr, (90), makes the interesting observation that the oedema is never deforming: if the face is involved, the features are not distorted as is true of nephritic /



A common type of case, shewing atrophy of the muscles of the arms. There is also atrophy of the leg muscles partially masked by oedema.

nephritic oedema.

Apart from the absence of albuminuria, another curious clinical point serves to differentiate the swelling from that occasioned by nephritis, and that is the fact that the oedema is markedly firmer than that of nephritis.

Free fluid may occur in the abdominal cavity and also in the chest, but usually not to any great extent unless there is accompanying heart failure.

All marked cases of wet "beri-beri" shew atrophy of the underlying muscles: they also have the same complaints as dry beri-berics. If a "wet" case leaves his bed, he will only be able to walk with difficulty, this being due to breathlessness, mechanical interference by the dropsy, and partly to paresis. He may exhibit foot drop, and if firm pressure be applied to the calf muscles through the oedema, he will certainly experience pain just as in the "dry" case.

The ankle and knee reflexes are absent and there is numbness of the fingertips, toes and shin bones.

In other words a patient with wet beri-beri is manifestly a "dry" case with oedema superimposed.

Cardiac Symptoms are almost always present in every case - both "dry" and "wet" - at some time during the disease.

Of these palpitation is the most common, and at the same time, the most annoying. It tends to be worse at night, or may come on after exertion; it may be slight or it may be severe and accompanied by such a degree of oppression /

oppression and breathlessness as to threaten impending dissolution. There are often also anginal symptoms and a sense of fullness in the epigastrium. Palpitation would appear to be the result of an actual increase in the action of the heart which shews itself by visible pulsation of the vessels at the root of the neck, of the praecordium and upper abdomen, despite the fact that at the same time the pulse may even be small and thready.

An examination of the heart will shew on percussion, enlargement of cardiac dullness, more marked to the right.

The apex beat will sometimes be found displaced downwards and outwards, so that though involvement is undoubtedly more definite on the right side, the left heart may also be enlarged.

On auscultation loud murmurs are often heard - usually systolic in time; the second sound over the pulmonary area is particularly loud and sharp, and may be reduplicated.

Embryocardia, too, may be observed; "the auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may hardly be possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration; so that the sounds of the heart are like the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and short interval like the beats of a badly-hung clock." (91).

THE ACUTE PERNICIOUS CARDIAC TYPE.

This condition is known throughout the East as shôshin; I was fortunate enough to observe and treat three such cases - fortunate, in that this fulminating illness is of infrequent occurrence as compared with the many other manifestations of beri-beri.

It is not seen in those patients, who exhibit nervous symptoms early, as this necessitates complete rest.

The symptoms are of sudden onset - in each of my cases, the picture was identical: I received an urgent signal to proceed at once to a certain ship. As I had at my disposal a fast launch, I reached all of these patients in less than two hours' time.

On arrival, the history was the same; the patient previously had not reported sick; while working he had been observed to collapse.

On examination dyspnoea was distressing in the extreme. The patients were very restless, tossing from side to side without relief and complaining of an agonising pain across the heart. The liver was enlarged, pulsating and tender in each case, and there was also oedema of the feet and ankles.

Hawes, (92), has stated that, if untreated, the pulse becomes smaller and smaller, the veins dilate, and the patient dies, with intense dyspnoea, but usually retaining consciousness to the end.

All three of my cases recovered: they received adequate /

adequate therapy as recommended by Hawes; improvement was immediate, and was reckoned in minutes.

INFANTILE BERI-BERI.

At first glance, the condition as observed in infancy appears to be quite different to that which we are accustomed to see in the adult. There are two forms - the acute and the chronic. If, however, we pursue our investigation further, we find that the acute form corresponds pretty accurately to the acute pernicious cardiac form of adult beri-beri, when we make allowance for the fact that the child is unable to vouchsafe any information as to its feelings. In the chronic variety too, the clinical findings closely resemble the manifestations of the adult "wet" case with the exception of the motor and sensory disturbances which constitute such an important factor in the picture of the condition, but which may easily be present in the infant without being demonstrable. "Dry" cases are also met with, but are probably often missed, as they may be difficult to diagnose.

Beri-Beri affecting breast-fed babies is still of quite common occurrence in Malaya.

Fehily, (93), has remarked that "food prejudice" in Hong Kong partly accounts for the large incidence of beri-beri. Most mothers believe the symptoms to be due to "fung" (wind) and therefore abstain from fruit and vegetables. They are less careful about female infants and therefore more males develop beri-beri!

In the Acute type, a young infant, who has apparently been fit and well, is suddenly seized with what the mother imagines to be wind, or colic. During the paroxysm, the child straightens out his body, and becomes perfectly rigid, the muscles of the abdomen being tense and hard. Gradually the face becomes cyanosed and the veins of the neck engorged.

On further examination the pulse is found to be small and rapid, the heart enlarged, again especially to the right: there may or may not be oedema, and the knee reflexes may or may not be elicited.

Some intercurrent infection was present in both my cases shewing this acute abrupt onset - pneumonia, and pyelitis complicated the pictures and were probably the precipitating factors.

If the case does not receive attention urgently, death occurs in less than 24 hours, following repeated paroxysms. I use the word paroxysm advisedly, as in no case were convulsions manifest. The word "convulsion" has crept into modern literature on the subject, I believe wrongly.

If the mother is questioned, she will admit to having had symptoms of beri-beri, and examination never fails to demonstrate that she is indeed suffering from the condition, itself.

Chronic infantile beri-beri shews itself first as a disturbance of the gastro-intestinal tract: there are feeding /

feeding troubles, constipation and vomiting being of frequent occurrence.

The child then becomes restless and fretful, especially at night, so that a good night's sleep is rarely obtained.

The characteristic so-called "aphonia" then occurs; it alarms the mother and rightly so, for it is an indication that the disease is serious and far advanced. Most descriptions refer to it as being a plaintive whine or moan, but the characteristic feature to me appears to be the somewhat cracked timbre of the note, and not the actual continual bleat itself.

By this time, the heart is usually affected; the impulse may be quite violent and rapid.

Enlargement of the right heart is marked, and the apex may be down and out. On auscultation, the heart sounds are extremely rapid, and of a regular character - it is impossible to differentiate the 1st and 2nd sounds.

There is dyspnoea, if the heart is involved to any extent, and oliguria is present in nearly every case.

There is a distinctive pallor of the skin with a contrasting cyanotic hue round the mouth which may be quite striking.

Oedema of the feet and ankles I have found to be almost constant, as is diminution or complete absence of the knee reflexes.

The condition in the past almost invariably ended /

ended in death if the mother continued to nurse the infant. In these cases, death was due to heart failure and evidently closely resembled the sudden cardiac attack which constitutes the acute form of the disease in the adult patient.

The outbreak of beri-beri amongst personnel of the Straits Settlement Royal Naval Volunteer Reserve, Singapore, April to July, 1941.

One morning in April, 1941 a Malay rating shuffled into my sick bay at H.M.S. "Laburnum", Singapore. It was at once obvious that he was suffering from beri-beri.

I immediately thought of various cases I had seen during the previous week or two; none of them complaining of anything very definite. Such symptoms, however, as constipation, anorexia, vague aches and pains, breathlessness, a tingling sensation in the fingertips or toes, or cramps in the calf muscles, had become more and more commonly reported.

In the next few days, quite a number of ratings came up with similar complaints and on examining them further, unequivocal signs of beri-beri were discovered.

The S.S.R.N.V.R. complement consisted of some 2,500 ratings, mainly Malays and Chinese - all had to be examined as quickly as was practicable.

When I had finished my close scrutiny, I was appalled at the number shewing signs either of frank beri-beri or of the subacute condition.

Histories were taken in all cases and it was found that most of the ratings were living on a diet which contained an abundancy of over-milled white Siamese rice: that, in addition they had dried fish every alternate day - more or less, a very inferior curry each day with but a sprinkling of vegetables, and on the days alternating with fish /

fish, a small amount of meat. This comprised their entire diet apart from white bread and coffee.

Conditions varied in the ships depending on the individual cook concerned: some prepared the food badly, destroying any vestige of vitamin B_1 which had been present: others fed the men very badly and pocketed the profits.

Dietetic reform was instituted at once: it consisted in the substitution for ordinary white rice, of grade I parboiled rice which was milled by the government in Bagan Serai; the substitution for white bread of reconstituted brown bread which had just been produced in Malaya but which had not, at that time, been popularised; the addition of vegetables with a high vitamin B content; the insistence on an adequate amount of butter being given to each rating; the substitution of one cup of marmite for coffee daily; and the urging that individual commanding officers should personally supervise the prosecution of these recommendations.

By August, 1941, beri-beri had been entirely eradicated, the incidence of intercurrent infections had been reduced, and the capacity for physical exertion had been greatly increased throughout.

During this outbreak, manifestations of deficiencies attributed to other than lack of vitamin B_1 were encountered: these were as follows:-

1. Eczema of the scrotum.
2. Cheilosis, Circum-corneal injection and corneal vascularisation.
3. Buccal, linqual and mucous membrane abnormalities.
4. Hemeralopia.

5. Anaemias - both macrocytic and microcytic.

6. Abnormal conditions of the skin.

Eczema of the Scrotum.

In two cases, this condition occurred as a clinical entity without other demonstrable signs of any deficiency. The skin of the scrotum looked raw and red: it was atrophic and fissured. There was considerable irritation productive of scratching.

It did not respond to either vitamin A or D(shark liver oil)administered locally or by the mouth. More important still however, was the fact that nicotinic acid failed to alleviate the condition, and it was only cured after administering marmite and yeast tablets.

In 1935, Landor and Pallister, (94), reported a condition characterised by "eczematous scrotal dermatitis", glossitis and stomatitis; later paraesthesias and weakness of the legs developed. They believed the disease to be due to lack of vitamin B_2.

Sebrell and Onstott, (95), demonstrated a scrotal dermatitis in dogs on a riboflavin-deficient diet.

Karunukaran and Nair, (96), recorded a condition which was undoubtedly occasioned by multiple deficiencies in an asylum at Travancore: scrotal eczema which occurred in most of the cases they believed to be due to lack of more than one factor.

My personal belief is that the condition is not a sign of nicotinic acid deficiency but is due to lack of /

of some other factor in the B_2 complex.

Eddy and Dalldorf, (87), have written that "in the rat, deficiency (of pantothenic acid) causes dermatitis of the snout and later of the genitalia." Lack of this factor may possibly, therefore, be the cause.

Goldberger, following experiments on human beings in whom pellagra had been induced, considered that scrotal lesions were frequently the first sign of pellagra.

It is important to realise however that just as pellagra is not merely the clinical expression of nicotinic acid deficiency alone, so beri-beri, though undoubtedly resulting mainly from lack of vitamin B_1, also manifests signs of other deficiencies as well.

2. Cheilosis, Circumcorneal injection and corneal vascularisation.

The above triad are now considered to be the result of riboflavin or pyridoxin deficiency and need no further comment. As would now be expected, they were cured by administration of marmite and yeast tablets.

3. Buccal, Lingual and mucous membrane abnormalities.

During the "outbreak" it was not infrequent that a Malay rating reported, complaining of a burning sensation in the mouth. On examination there was a reddened appearance of the papillae over the anterior third and tip of the tongue. It was obviously painful and there was also a certain amount of salivation.

Aphthous /

Aphthous ulcers were found in some cases on the buccal mucosa. It is interesting to note that a similar condition occurred in four European patients. The ulcers were resistant to treatment with the usual caustics and only responded to nicotinic acid therapy.

Nicotinic acid also proved a dramatic cure of Vincent's Angina affecting three English women in Singapore. In each case the condition was characterised by extreme inflammation of the fauces and fever of 103°F. In 24 - 36 hours the improvement was marked, and in a week, the patients were cured. At H.M.S. "Lochinvar" we are still encountering numerous cases of Vincent's Angina. Surgeon Lieutenant Buchanan, R.N.V.R., (97), considered ascorbic acid to be of use in the treatment: I maintain however that nicotinic acid is of greater value, and all cases are now receiving this form of therapy.

4. Hemeralopia.

Night blindness was spontaneously reported in three cases: vitamin A did not appear to result in any improvement until the vitamin B complex had been prescribed.

For some time, vitamin A was thought to be the only food factor of importance in the prevention of hemeralopia. Stewart, (98), has shewn that vitamin C is also implicated, and Kimble and Gordon, (99), have suggested that riboflavin is necessary for the absorption of vitamin A from the gut.

5. Anaemia.

A low colour index anaemia was commonly found in the ratings during the time of the outbreak of beri-beri: it responded /

responded to iron therapy.

Two cases, however, suffering from beri-beri showed a high colour index anaemia with macrocytosis. This failed to respond to thiamin but was quickly cured by the administration of large doses of marmite.

In private practice, macrocytic anaemia was also observed in five British women who were pregnant. Marmite again constituted a cure - liver was not administered.

Text books tend to confuse one on the subject of Tropical macrocytic anaemia: I consider that the condition in itself is an entity. I believe it to be due to a deficiency of some essential component of the vitamin B_2 complex, as yet not differentiated: there is evidence to shew that this factor is not riboflavin, nicotinic acid, or pyridoxin.

The condition frequently occurs complicating pellagra, sprue, beri-beri and pregnancy.

It is wrong to describe a haemolytic form - haemolysis does not occur in this condition unless there is an accompanying malaria: in other words, there may be primarily, or potentially, a nutritional deficiency to which is super-:added a haemolytic agent - the malaria parasite.

Most of the work on this subject has been carried out by Wills, (100), (101), (102), (103), who, as long ago as 1933 stated that "in the majority of cases, even those with counts as low as one million, the response to marmite in adequate doses is so rapid that the more expensive treatment is rarely necessary."

This /

This deficiency may result through

1. actual lack of the factor in the diet,
2. gastro-intestinal lesions either interfering with the absorption of the vitamin, or causing its destruction, (104),
3. liver insufficiency, (105),
4. a temporary depression of secretion of the specific intrinsic factor of Castle, (106),
5. diversion to the foetus of the anti-anaemic principle itself, (107).

Two recent papers are worthy of mention in connection with the aetiology of macrocytic anaemia occurring in deficiency states.

Elsom Lewy and Heublein, (108), in 1940 studied the results in a volunteer who consumed a diet deficient only in the vitamin B complex. They have stated that

"Decrease in the number of red blood cells, increase in mean cell volume and haemoglobin, macrocytosis and polychromasia occurred." This was "uninfluenced by the administration of thiamin or riboflavin, but was relieved after the subject had received a general diet and brewer's yeast for 4 weeks."

Williams and Mason, (29), who recently conducted thiamin deficiency experiments - eleven white women being the subjects chosen - found that "A considerable degree of anaemia was observed in five instances. The anaemia (3,000,000 to 3,500,000 erythrocytes/cub. mm) tended to be hyperchromic and macrocytic in type and in three instances was associated with /

with development of achlorhydria.

The anaemia was not relieved during the period of restriction of thiamin by providing additional amounts of iron, copper and protein or by administration of crystalline riboflavin, nicotinic acid, pyridoxin, pantothenic acid and choline..... The haematologic response of two subjects who had anaemia to unheated brewer's yeast and liver extract in large amounts administered orally and parenterally was no better than the response of two subjects to thiamin chloride alone."

This may be so, but I feel convinced that it will not be long ere a specific haematogenic factor itself is isolated, possibly from a substance such as marmite.

Abnormal conditions of the skin.

A few of my cases of beri-beri shewed: (a) a dryness of the skin, (b) a roughness, which was most marked about the knees, front of thighs and elbows, (c) an absence of sweating.

This was associated with the perlèche of riboflavin and pyridoxin deficiencies, and the scrotal eczema of unknown deficiency origin.

The condition was cured by the administration of nicotinic acid.

It is interesting to note that Frazier and Hu, (109), described dryness of the skin as a manifestation of vitamin B deficiency.

This condition, which was characterised by a dry /

dry, rough skin, a papular eruption over the front and sides of the thighs, over the posterior and lateral sides of the forearms, and just below the elbows and fronts of the arms and shoulders, was described by Nicholls, (110) as Phrynoderma or Toad's skin.

It has been observed, (20), however, that there "is still some uncertainty as to whether toad skin is due to a simple deficiency of vitamin A or whether some other factors are involved."

It is considered possible that vitamin A deficiency is primary and that nicotinic acid is an adjuvant in the aetiology of phrynoderma.

It should not be forgotten that the derivation of Pellagra is pelle = skin, and agra = rough; and that this condition responds to nicotinic acid therapy.

THE CLINICAL DIAGNOSIS OF BERI-BERI.

Frank Beri-Beri is generally easily recognised, but individual cases can present great difficulties, especially when there is no oedema or cardiac involvement: such cases closely resemble the common neuritides. It must also be remembered that beri-beri is a syndrome and that there may be accompanying signs of deficiencies other than those of vitamin B_1 lack alone.

The most common early complaints which lead one to suspect beri-beri are as follows:-

1) Indigestion,
2) "Pins and needles" affecting fingers and/or toes,
3) Inability to carry out any task involving extra expenditure of energy,
4) Breathlessness,
5) Palpitation,
6) "Kaki bengkak" (swelling of the feet).

Platt and Lu, (48), have attempted to tabulate the major symptoms of beri-beri with the degree of vitamin B_1 deficiency. Certain comments are, however, necessary.

"Beri-Beri: The assessment of symptoms

in /

in Human Beings in terms of Vitamin B_1 Deficiency."

Clinical symptoms	Vitamin B_1			
	+	++	+++	++++
Neuritis, usually of legs with altered (usually absent) knee and ankle jerks,				
Paraesthesia,				
Weakness,				
Oedema,				
Enlarged heart,				
Tachycardia (with embryocardia),				
Cyanosis,				
Dyspnoea,				
Cardiac Decompensation,				
Epigastric distress,				
Prostration and restlessness				

Comments:-

1. Ankle-jerks are lost before the knee reflexes.
2. Tachycardia does not occur.
3. Cyanosis, is only observed on rare occasions and then as an extremely late manifestation.
4. Enlarged heart, might with advantage be altered to enlarged right heart.
5. Epigastric discomfort and loss of appetite should be mentioned as early signs, and
6. Oedema ought also to be included in the first group.

Meyers, (78), believes that thiamin deficiency occurs (a) as a simple polyneuritis and (b) as beri-beri (polyneuritis, oedema, and cardio-vascular dysfunction). In about /

about half his cases of polyneuritis without oedema, heart function was quite normal: in the cases with oedema, 92% had heart symptoms.

My observations would confirm this statement regarding the common involvement of the heart in cases shewing oedema, but I feel that it is unjustified " quibbling" to attempt to differentiate polyneuritis from beri-beri. For over a century now, it has been customary to use the word beri-beri to embrace both the dry and the wet forms of the condition. Until we are able to correlate each individual symptom and sign with the exact dietetic factor involved, it would appear to me to be preferable to retain our previous conception.

When it was observed that oedema occurred in certain cases as an early manifestation of beri-beri, it was at once considered that possibly the occurrence of oedema of the feet and ankles, complicating pregnancy in British and European women, resident in Singapore, was simply a deficiency manifestation. Thiamin parenterally and marmite orally were administered to six such cases, three of whom also had small patches of anaesthesia over the tibiae: the oedema rapidly disappeared in all six, as did the sensory disturbance in those affected.

I have often observed frank beri-beri in Malay, Chinese, and Indian women - most marked in the latter half of pregnancy and in the puerperium. It is my contention that British women in the Tropics, if not at home as well, may /

may shew signs of the incipient condition.

In this connection, I would quote from Nixon's article in the British Medical Journal of May, 16th, 1942, (111).

"Fulminating Beri-Beri is a rare complication of pregnancy in this country. It is possible that subcritical - a term which we prefer to subclinical - states of avitaminosis B_1 do exist among some pregnant women. In Hong Kong there is a poor Chinese population in which avitaminosis B_1 is endemic.

Early in pregnancy such women complained of cramps, pins and needles, fatigue and oedema, just as our women do.

Westenbrink and Goudsmit, (1938), have shewn that women of the poor part of Amsterdam - wives of unemployed - had a high incidence of these symptoms than their non-pregnant sisters or pregnant women of the better class. Analysis of their diet shewed that the food intake was much less, especially as regards brown bread."

He concludes:-

"In view of these findings, and the occurrence of oedema and suppression of urine in eclampsia, offering a striking similarity to the clinical picture of beri-beri, it is suggested that vitamin B_1 therapy might be beneficial to such patients."

In the diagnosis of beri-beri, the following signs, I consider are most important.

1. The areas over the anterior surface of the tibiae which are anaesthetic to pin-prick.

2. The hyperaesthesia of the calf muscles.

3. Loss of ankle and knee reflexes.

4. Oedema.

5. Shuffling gait (more common than the so-called characteristic steppage gait).

6. Enlargement of the right side of the heart.

7. Cardiac murmurs, especially systolic (rheumatic carditis is a rarity in the tropics).

The following special tests have been employed recently to confirm the diagnosis.

1. Determination of vitamin B_1 deficiency.

One can now find out the actual amount of this vitamin in the blood and urine. Estimation of the blood carboxylase content, and also the amount of pyruvic acid in blood or in urine can assist in the diagnosis of vitamin B_1 deficiency. Finally, in addition to these direct methods, determinations of the tissue saturation with vitamin B_1 may be carried out, whereby the effects of certain doses of vitamin B_1 are measured before and after administration.

(a) Blood Tests.

The determination of vitamin B_1 in the blood is difficult, inasmuch as the normal concentration is minute, approximately 1 γ in 100 ml; furthermore according to Goodhart and Sinclair, (42), haemolysis of the blood vitiates the results.

The /

The growth rate of Phycomyces as devised by Schopfer, (112), has, however, been found useful, though it must be mentioned that there are also other factors in blood which influence the growth of this fungus.

Since ninety per cent of the vitamin B_1 present in the blood is in the form of pyrophosphate or carboxylase, estimation of the latter gives an indication of the degree of vitamin B_1 deficiency. This assay can be carried out with relative ease and a value of 3γ or less (normal = 7γ) per 100 ml. is considered to be proof that a state of deficiency exists. The pyrophosphate occurs exclusively in the blood cells, therefore this test is only to be used where there is no accompanying blood dyscrasia.

A marked increase in pyruvic acid content of the blood has been found in man and pigeons suffering from lack of vitamin B_1. Either of two methods of assay may be adopted for determination of pyruvic acid. The first is based on the isolation of sodium pyruvic - 2, 4 - dinitrobenzoate, and the red colour developed with the addition of strong alkali. This method is now specific as other alpha-keto-carboxylic acids also give the same reaction. The second assay procedure consists in the estimation of bisulphite-binding substances, (47). The normal pyruvic acid content of the blood averages 2.8 mgm. per 100 ccs.

(b) Urine tests.

The urinary output of vitamin B_1 is closely related /

related to the nutritional state of the body. An average daily excretion varies between 50 and 150 γ vitamin B_1, (67). It has been demonstrated that figures are lower in B_1 avitaminosis, (113).

For the actual determination of vitamin B_1 a number of different methods have been described. One of the most satisfactory of these appears to be the bradycardia assay originally suggested by Drury, Harris and Maudsley, (114). This method has however, been criticised because the heart rate of rats is affected, not only by thiamin, but also by the concentration of adenylic acid, and because bradycardia can be produced in rats simply by restricting the food intake even if the supply of vitamin B_1 is adequate.

The Thiochrome method described initially by Jansen, (115), has been modified recently, as urine contains fluorescent compounds which interfere with the thiochrome determination, (116): it has been successfully applied, especially when larger quantities of the vitamin are assayed as in saturation tests.

The Diazo colorimetic test of Prebluda and McCollum, (117), is believed to be specific for vitamin B_1.

A yeast fermentation method of assay has also been applied and is held to offer promising results for urine tests, (118).

Urine contains other substances which stimulate the fermentation, and it has therefore been recommended that determinations should be carried out, before and after oxidative /

oxidative inactivation of the vitamin.

The content of pyruvic acid may be investigated as described in blood tests, but so far the actual amount present in the urine of the normal and B_1-deficient man has not been ascertained.

In rats the amount excreted increases during vitamin B_1 deficiency by 200 - 400%.

Unfortunately none of these tests were being applied in Singapore in 1941; however, they are undoubtedly of sufficient interest and importance to merit inclusion.

2. Aalsmeer's adrenalin test, (75).

On administering adrenalin to a patient with beri-beri.

(a) A rapid fall in the diastolic pressure is said to be characteristic, and

(b) an audible sound develops in the antecubital fossa if not already present.

As adrenalin evidently tends to precipitate shôshin, it was considered inadvisable to adopt this test.

3. Volhard's diuresis test. The patient is given a litre of water to drink and the amount of urine which is voided in 4 hours is charted. Normally all this fluid should be excreted: but in some of my cases of beri-beri, I found that there was as much as a pint retained at the end of this period.

4. For my own interest, I made those of my patients who were not serious ill drink two pints of water and then run a distance of about 240 yards in the heat of the tropical sun. /

sun. They did not perspire as much as normal individuals who were given the same test as controls. Individual variations occur normally in the amount of sweating, but I am convinced that in many of my cases there must have been an atrophy of the sweat glands. This dry skin has been referred to earlier.

5. Electrocardiograms were taken in cases shewing signs of heart involvement. The tracings varied from normality to

a) shortened P-R intervals,

b) inverted T waves,

c) low voltage deviations,

but nothing was observed, which in any way could be described as characteristic.

Dustin, Weyler and Roberts, (119), have summarised the electrocardiographic findings of various authors as follows:-

"Aalsmeer and Wenckebach - Tachycardia and shortened conduction time (P-R interval 0.12 sec. or less).

Scott and Herrmann - Negative T_1 and T_3. Some with right and some with left ventricular preponderance. Low voltage and slight disturbances in ventricular complexes.

Keefer - negative T waves, right and left preponderance and low voltage.

Weiss and Wilkins - Abnormal T waves, prolonged electrical systole (Q-T) and sinus tachycardia.

Feil - Inverted T waves. Prolonged systole.

Dustin, Weyler and Roberts - Increased electrical systole. Rapid rate. Low voltage and flattening of T wave /

T wave in first three leads.

6. X-rays. Some few cases were x-rayed but it is considered that only in infantile beri-beri is roentgenology of any assistance: then it may be of use to visualise the actual enlargement of the right side of the heart.

"Cardiac enlargement has been measured in 200 cases by Kobayashi using x-ray measurements. He found that the lung-heart quotient of Groedel is reduced from a normal value of 1.71 to between 1.12 to 1.43 in beri-beri. The method was recommended as an aid to diagnosis." (87).

7. Circulation time.

It has been known for some time that in certain cases of beri-beri the circulation time is reduced.

Deficiency of iron and of certain protein derivatives essential for normal blood formation produces through hypochromic or macrocytic anaemia, changes in the circulation. These changes are characterised mainly by an increase in the velocity of the blood flow and cardiac output, and by a fall in the arterial pressure, (76).

Circulation Times in a series of my cases were determined by the intravenous injection of histamine (0.001 mgm. histamine phosphate per kilo body weight) and noting the time at which flushing of the face, due to capillary dilatation, occurred.

Those patients who were anaemic shewed a marked increase in the velocity. The average time of normals (arm to face) was 25 seconds: some cases of beri-beri shewed a decrease to as short a time as 10 seconds.

It is not considered, however, that observations on circulation time can in any way assist the diagnosis of beri-beri.

8. Exercise Tests.

Most of the tests hitherto described are complicated, and it was considered that some simple clinical test might be of use in the diagnosis of early beri-beri.

If a patient with beri-beri squats upon his heels - a position which most Orientals find extremely comfortable - he may experience pain, especially in the calf muscles, and find difficulty in rising without the aid of his hands. This has been known for many years as the "jongok" or squatting test, and is certainly of some value.

Two exercises were given to all ratings examined during the outbreak of beri-beri and I firmly believe that they are of considerable use in diagnosis.

It was discovered that the worst cases were unable

1. to hold their breath, and
2. to keep their arms horizontal, for more than a few seconds.

Healthy Malays and Chinese were able to hold their breath for about 1 minute. The worst cases of beri-beri could only do so for 7 seconds and those shewing signs of the sub-acute condition for not longer than 15 - 20 seconds.

Likewise, severe beri-berics could not keep their arms above the horizontal for longer than 12 seconds, and the mild /

mild for longer than about 25 seconds at a time, whereas healthy ratings could continue for minutes.

These two tests are extremely simple and I consider that they are worth while trying in every case, not fully developed and difficult to diagnose. It is essential to explain to the patient that he must try to hold on for as long as possible, and to have a "control" performing the test at the same time, to act as a stimulus.

Proof that these tests are of use is evidenced by the fact that cases shewing "decreased tolerance" initially were, when cured of their condition by treatment with vitamin B_1, enabled to hold their breath and retain their arms in the horizontal position for normal periods of time.

In arriving at a diagnosis, the following conditions must be differentiated.

1. Tabes Dorsalis: evidence of syphilis,
Wassermann reaction,
"lightning pains",
characteristic sensory signs,
pupillary abnormalities.

2. Alcoholic neuritis: tremors.
predominance of mental symptoms and the fact that the class of people who are rice eaters are seldom drinkers.

3. Lead Palsy: infrequent occurrence,
blue line upon gums,
punctate basophilia,
colic,
arms most commonly affected.

4. "Malarial Neuritis": probably due to associated deficiency of vitamin B_1. Demonstrat-:ion of parasites in blood.

5. Ankylostomiasis: This condition is so common, that in any patient suffering from what appears to be beri-beri the stools must be examined for hook worm ova.
severe anaemia,
no paralysis, loss of reflexes or anaesthesia,
eosinophilia.

6. Heart /

6. Heart failure: No loss of sensation, or reflexes or power of movement.

7. Nephritis: indicated by albumen and casts in the urine,
no loss of sensation, or reflexes.

8. Lathyrisim: in Abyssinia, Algeria and India - does not occur in Malaya,
history of eating Lathyrus sativus,
knee jerks increased, no tenderness of muscles, no paralysis or anaesthesia.

9. Oedema of mustard-oil poisoning:
A peculiar form of epidemic dropsy, as seen in India and other Eastern countries: distinguished from beri-beri by purplish-red mottling of skin of legs; also retinal haemorrhage and lung signs, (120, 121).

VITAMIN B_1 REQUIREMENTS.

There have been - and still are - certain difficulties in attempting to assess how much vitamin B_1 a man needs daily.

It is obvious that a minimum protective dose will be entirely different to an optimum amount. Experimentally it has been observed that rats do not develop polyneuritis if they receive 1 - 2 γ. of crystalline vitamin B_1, per day, but that growth on this amount is limited and only increases normally when about 100 γ. are given.

Japanese workers list six factors as predisposing to beri-beri:

1. Temperature. Cases are commonest in the warm months. This seems independent of fluctuations in the thiamin content of the food.
2. Humidity. Both military and industrial records shew that high humidity predisposes individuals to beri-beri.
3. Age. It is a disease of young people, the majority of the patients being between 15 and 30 years of age.
4. Sex. Males are affected 2 or 3 times as often as females.
5. Robustness. Active individuals seem to be predisposed to beri-beri. Scheube noticed this in 1894. Army records shew that forced marches precipitate attacks. Shimazono observed 8 cases among girls working in a spinning plant. They sat at their machines and worked almost entirely with their left hand. All had hyperaesthesia of that part of the body and /

and no other.

6. Physiological strain. Pregnancy, lactation and infectious diseases may precipitate beri-beri. McKenzie ascribes one case to hookworm infestation and the loss of blood due to the parasites, (122).

An extra amount of vitamin B_1 is therefore indicated in the Tropics;

a) during the warm months,

b) when the humidity is high,

c) in active adolescents,

d) in pregnancy, lactation, and debilitating illnesses.

Jolliffe, (123), gives a comprehensive table of factors which increase the need for vitamin B_1:

1. Increase in Total Metabolism,

A. Abnormal activity, as associated with:

1) Prolonged continuous activity.

2) Delirium.

3) Manic depressive psychosis, manic type.

B. Fever, especially of long duration, as in

1) Tuberculosis.

2) Typhoid.

3) Malaria.

C. Hyperthyroidism:

D. Pregnancy:

E. Rapid growth:

2. Faulty Assimilation,

A. Diarrhoea, especially of long duration, as in

1) Ulcerative and mucous colitis.

2) /

2) Intestinal parasites,

3) Intestinal tuberculosis,

4) Sprue.

B. Gastro-intestinal fistulae

C. Diseases of gall bladder and liver

D. Achlorhydria

E. Carcinoma of the stomach.

3. Increased Excretion,

A. Polyuria, as in

1) Uncontrolled diabetes mellitus

2) Diabetes insipidus

3) Long-continued excessive fluid intake, as in urinary tract infections

B. Lactation.

That exercise accelerates the onset of vitamin B_1 deficiency has been conclusively demonstrated by Plimmer, (124), and later by Cowgill, (125).

It is interesting to note that when beri-beri has occurred in ships, stokers have been affected to a greater extent than seamen, owing to the greater physical exertion of the former and the conditions in which they work.

One of the first attempts to assess the daily requirements of vitamin B_1 was made by Cowgill, (125) who described the following formula:

Minimum daily vitamin B_1 requirement (in mgm. equivalents) = daily calorie intake x 0.0284 x weight in kilos.

Now /

Now since 1 mgm. equivalent = 0.05 I.U.

therefore minimum daily requirement in I.U. =

daily calorie intake x 0.0284 x weight in kilos x 0.05.

From this formula the minimum daily requirement for an average adult would be about 300 I.U.

Baker and Wright, (126) have made a thorough survey of the problem, and have compiled the following table from a study of various diets:-

"Vitamin B_1 Content of Various Diets."

	Daily intake of vitamin B_1 I.U.
Diets on which beri-beri has resulted	71 - 382
Diets on which beri-beri has been prevented	145 - 500
B.M.A. "bare ration" (admitted to be low in vitamin content)	212
B.M.A. "individual diet No. 2" (good working class diet)	440
B.M.A. "child's diet (3 - 6 years)"	298
Childrens' diet, poor law homes (Ministry of Health Committee)	450
Child's diet, after Simmonds (3-6 years)	376 - 393
" " " " (11 years)	606 - 657
High vitamin diet	872 - 1,012
" " " (Simmonds)	693
Diet for toxaemia of pregnancy	1,520

It must be mentioned that Williams and Spies, (34), disagree with Cowgill's formula in principle. They believe that the fundamental relationship is between vitamin B_1 and carbohydrate or non-fat calories. They state that /

that "Viewed in the light of all the facts, the poorer populations of the United States appear to owe their freedom from beri-beri as much to the relatively liberal fat content of their food as to a greater liberality of thiamin supply, as compared with the people of the Orient."

They consider that the ratio of I.U. of vitamin B_1 to the number of non-fat calories in the diet should not be less than 0.25 for the prevention of deficiency, and that 1,330 I.U. represents a true optimum.

Moran and Booth, (127), state that the national average in the United Kingdom of vitamin B_1 per head per day is 376 I.U. They assert that a desirable average would be approximately 700 I.U. per head per day. It is interesting to note that a hundred years ago wholemeal bread alone probably contributed some 500 I.U. of B_1 to the daily diet. The implication is obvious.

Bicknell and Prescott, (20) have summarised the position with regard to vitamin B_1 requirements very aptly; they state that "To cover the needs of all individuals an optimum intake of 20 - 25 I.U. per 100 calories should be aimed at. Assuming that the daily calorie consumption is 2,810, the optimum vitamin B_1 requirement becomes 560 - 700 I.U. daily. Young children require more in proportion to their weight, and pregnant and nursing women require from two to five times the minimum vitamin B_1 requirement."

PREVENTION AND TREATMENT.

Thirty years ago Vedder, (31) wrote "we may justly claim that within the past few years we have mastered the subject from a practical point of view. We are now in a position to prevent the disease in any community that can and will follow our advice just as surely as we can prevent smallpox and yellow fever".

Yet the control of beri-beri still constitutes one of our major problems in the Far East.

A tremendous step forward occurred, however, when the Federated Malay States and Singapore interdicted the use of polished rice in their hospitals, schools and gaols.

Another important development took place in 1941, the introduction of bread to which vitamin B_1 had been added. As far as I can remember about 0.2 gm. of the vitamin was added to a 280 lb. sack of flour.

In endemic areas, prevention should take the form of the following recommendations:-

1. **education.** There was a considerable amount of opposition amongst the ratings in Singapore when I introduced parboiled rice. At first a compromise was arranged whereby they were given white rice and parboiled on alternate days.

However, by obtaining the co-operation of patients who had been cured of their beri-beri, and by reasoning with the more intelligent members of our complement, the ratings soon came to believe that the "Tuan doctor's nasi ubat" (medicine rice) was good for them and it was not long before, of /

of their own accord, they asked that they be given only parboiled rice.

2. popularisation of (a) parboiled rice and (b) fortified bread throughout the country: introduction of "food yeast".

Recently an Exchequer grant of £25,000 has been made in order to further a large scale experiment on "Food Yeast" in Jamaica. It has been known for some time that micro-organisms build up all the B vitamins, and contain a protein nutritive value as high as that contained in animal tissues. At the Chemical Research Laboratory of the Department of Scientific and Industrial Research, investigat-:ions were carried out to determine the most suitable organism which could be produced cheaply, would reproduce rapidly, and be harmless to man. Waste molasses to which nitrogen was added in the form of ammonium salts was considered to fulfil the necessary requirements. This product which is known as food yeast contains:-

high grade protein	50%
vitamin B_1	20 Microgrammes per gramme
riboflavin	60-80 " " "
pantothenic acid	60 " " "
nicotinic acid	400-450 " " "

"When dried it is a flaky substance, light straw in colour, and has a slightly meaty taste. It can be mixed with water or milk, added to soups and stews, and can be incorporated into biscuits and into flour for the daily loaf", (128).

This /

This preparation would be of the utmost value in tropical countries such as Malaya where the native diet is invariably lacking in B vitamins and high-grade protein.

3. emphasis on the value of suitable vegetables, kachang hijau, pork, liver, eggs, milk and fruit.

4. instructions on the preparation of rice and foods containing the vitamin. As vitamin B_1 is water soluble, a large amount of it is lost when the water in which the foods are cooked is discarded. This was could be used for soups to which marmite for instance could be added.

There were many vaunted cures for beri-beri in Malaya. Thus,

in Pahang: mistletoe leaves and "mambul" (Milletia servicea) were boiled, and the fluid used to bathe the limbs.

in Perak: "Keremak Bukit" (Altermanthera sessilis) and "bawang merah" (a local red onion) were used as a lotion.

in Kedah: the crushed leaves of the "Sembong" (Blumea Balsamifera) were used.

Elsewhere leaves of "kechubong" (datura) were expressed and the resulting fluid used as a lotion for beri-beri during pregnancy.

Another cure which evidently was "not specific" as it was used also for scabies or itch, was obtained from "kayu lada" (Ervatamia cylindrocarpa) which was pounded with broken rice.

One /

One of the most fashionable remedies consisted of a paste which was made from "maman hantu" (Gynandropsis pentaphylla), with cloves,

wild peppercorn,

a nutmeg,

turmeric,

"chabai tali" (Helicteres Isora),

cubebs,

and datura leaves.

Coarse lime was sprinkled on the paste which was then steeped in vinegar and warmed gently over a fire. A little oil was rubbed on the affected limbs, the paste then applied, and the limbs wrapped up in datura leaves. This treatment was repeated for three successive nights, (129).

The cure of beri-beri is now relatively simple: the introduction of thiamin has revolutionised treatment.

In the extremely mild subacute case, I found that 5 - 10 mgms. of thiamin chloride in tablet form daily, was sufficient to clear up the condition (1 mgm. is equivalent to 333.3 I.U.).

In cases of moderate severity, I found that optimum results were obtained when, in addition to improved diet and oral therapy, 10 mgms. of thiamin were injected daily usually for 10 - 14 days.

It is often stated that in those cases shewing oedema, /

oedema, saline aperients should be given: I found this treatment contra-indicated: it upsets still more the gastro-intestinal tract, and moreover the oedema disappears very quickly once "specific" therapy has been instituted.

Rest is of course essential in all but the mildest cases.

Hawes, (92), was the first to demonstrate the cure of shôshin. After failing with enormous doses of vitamin B_1 orally, he found that 3,000 - 5,000 units intravenously resulted in dramatic improvement.

He concluded that

" 1) the reaction is quantitive, the vitamin is non-toxic.

2) The effect of one dose is lasting.

3) It must be given by injection to have any rapid effect.

4) The diagnosis of a pure B_1 deficiency can be confirmed by an injection of an adequate amount of the vitamin, and the response to treatment is very rapid.

In England, this may be important in children in whom I suppose the pure deficiency is most likely to occur."

I gave each of my three cases 5,000 units intravenously: in a few moments, each one became less restless, the cyanosis and dyspnoea disappeared, and the patient became comfortable.

Most descriptions state that if there is right-sided cardiac failure (which is actually of constant occurrence in these cases) venesection is of great value. In none of my patients did I consider venesection indicated: the blood pressure already was extremely low.

Oxygen /

Oxygen may be of value, but as my cases occurred at sea this was not practicable. Diuresis occurred in all three, some 24 - 36 hours afterwards: (I believe however, that occasionally anuria may set in and death then supervenes with symptoms of uraemia).

After the first injection, 1,000 units were given hypodermically daily for 7 - 10 days, by which time each patient was fit for discharge.

One of two infants suffering from acute beri-beri died as I entered the room - this was the case referred to earlier. The second recovered. This baby was 4 months old and 1,000 units were given intravenously: thereafter the same amount was given hypodermically for 5 days. The baby was weaned as the mother was also suffering from beri-beri, and half a teaspoonful of Ryzamin B given orally twice a day. The pyelitis responded to sulphanilamide therapy and the infant made an uninterrupted recovery.

In Nauru, (130), "toddy" has been the remedy of choice - the dosage being

½ a drachm twice daily 1st month.
1 " " " 2nd month.
1 " three times daily 3rd to 6th months.

In the Phillipines "tiqui-tiqui", an extract of rice polishings, consisting of pulverized pericarp and aleurone layer has been found efficacious. Twenty minims are given as a dose, up to a total of 1 drachm a day in the average /

average case. If severe, double doses are given.

Under modern conditions, however, thiamin is obviously the treatment of preference. Two to three mgms daily are recommended for infants, in the form of crushed-up tablets in milk.

Other associated deficiencies, it must be remember-:ed, are usually met with and must be treated as they occur.

Marmite is most important as an adjuvant to the diet; its composition is as follows, (131).

I - Organic Matter (g/100 g).

Total Nitrogen	...	...	- 6.35
Total Protein x	...	...	- 10.00
Purine Nitrogen	...	...	- 0.356
Fat	...	...	- Trace
Carbohydrate	...	...	- Nil

II - Inorganic Constituents (Mg/100 g).

Sodium	...	...	- 6130
Chlorine	...	...	- 7750
Potassium	...	...	- 3440
Calcium	...	...	- 77.3
Magnesium	...	...	- 276
Phosphorus	...	...	- 1890
Sulphur	...	...	- 382
Iron (total)	...	...	- 5.2
Copper	...	...	- 1.96

Calories 41 per 100 g.

Acid base balance 171 cc. N/10 Alkali per 100 g.

x Protein Nitrogen x 6.25.

Apart from haematopoietic principles marmite also contains, (132):-

1) Vitamin B_1

The /

The difficulties in estimating vitamin B_1 in a foodstuff such as marmite are considerable and conflicting results have been obtained by using different methods of determination. Thus, samples tested by the pigeon method were were found to contain 30 I.U. of vitamin B_1 per gramme: more recently an average sample tested by the thiochrome method assayed 10 I.U. per gramme.

2) Nicotinic Acid.

Work at the nutritional laboratory at Cambridge has shewn that marmite is an exceptionally rich source of this substance, containing 64 mg. per 100 g., (133).

3) Riboflavin.

Marmite has been shewn to contain 3.30 mgm. riboflavin per 100 g., (134), and it has been used with conspicuous success in the treatment of riboflavin deficiency induced experimentally in man, (95, 135).

4) Pyridoxin and Pantothenic Acid.

As yeast is known to be a good source of both pyridoxin and pantothenic acid, it seems probable that marmite is also rich in these components.

Marmite is an extract made from fresh brewer's yeast (Saccharomyces Cerevisiae) by a process of autolysis. A small amount of vegetable flavouring is added.

Brewer's yeast is of course one of the richest known sources of all the vitamins of the B group and it is believed that marmite retains all these factors.

It seems reasonable to suppose that the beneficial action /

action of marmite may be due largely to the combined action of these components together with protein degradation products. Although it has not yet been substantiated, the vitamin constituents may prove to be interdependent and the effect may be synergistic.

The doses of marmite recommended in various conditions may be represented in tabular form:-

Disease	Daily Dose
Mild beri-beri and Vitamin B deficiency	½ to 2 ounces.
Infants	½ to 1 ounce.
Pregnancy in the Tropics	
(Europeans)	1 to 2 drachms.
(Natives)	2 to 3 drachms.

R I C E.

"Rice forms the staple food of nearly one half of the world's population: it is estimated that there are about 200 million acres of land under rice cultivation." (136).

Rosedale, (137), in 1939 compared for their nutritive value, husked rice (from which the outer hard, fibrous coat had been removed but where no polishings had been carried out) and polished rice.

He found that

Husked Rice: 21.4 oz. equiv. to 2,200 cals. produces 53 gms. protein.

Polished Rice: 21.4 oz. " " " cals. produces 38 gms. protein.

He also stated that husked rice contains 1/10th amount of Vitamin B_1 compared with yeast, and of course polished /

polished rice contains practically nil.

As 58 gms. of protein is considered an adequate daily amount of protein for the native population of Singapore - a diet of husked rice should almost supply the protein requirement.

Rosedale then tested a number of foods representative of those eaten in Singapore as supplements to a polished rice diet, but in no case could the difference between the two types of rice be bridged by any supplementary foods ordinarily available.

He added that "It remains for administrative authorities to educate the people as to the value of unpolished rice."

The following are the types of rice used by the population of Malaya.

1.) Siamese or Bangkok.

This is the staple rice known throughout Europe and America. It is white, clear, hard and dustless: it is not parboiled in the husk as types (2) and (3) but is sun-dried in the husk, threshed and then bagged.

It is used by Europeans, Chinese and Malays.

2.) Kedah or Penang.

This rice is grown chiefly in Kedah or the Krian district of Perak. Properly prepared it should resemble (3) but is usually produced carelessly and has a nauseating smell when cooked.

This padi is brought to Penang where it is steeped in /

in large cement vats, for anything from 36 - 72 hours. Fermentation occurs and the padi is then put into drums and subjected to the action of steam. It is later dried so that the husk can be removed easily.

3) Bengal or Negapatam.

This rice in Malaya is used by the Tamils and Cinghalese. The padi is soaked in its husk for 12 hours, boiled for $\frac{1}{2}$ to $\frac{3}{4}$ hour, dried in the shade for one day and again in the hot sun for another full day. When thoroughly dry, the husk is removed leaving a light-brown, semi-transpar-:ent, firm, sweet-smelling, oval grained rice.

Braddon long ago remarked that Tamils escaped beri-beri because they used Indian or Penang rice, and the Chinese contracted it because they used Siamese rice.

4) Rangoon.

This rice is prepared as (1) but is largely composed of the mill refuse and is used only by coolies.

5) "Pulut"

This takes its name from the fact that it is used with sugar to make sweet cakes: it is a whole-grained rice, but when boiled coalesces into a soft gelatinous mass.

6) This rice is really chips of type (1). "Cungee" is made from it and is a favourite breakfast dish with the Chinese. "Samsu" is also distilled from it.

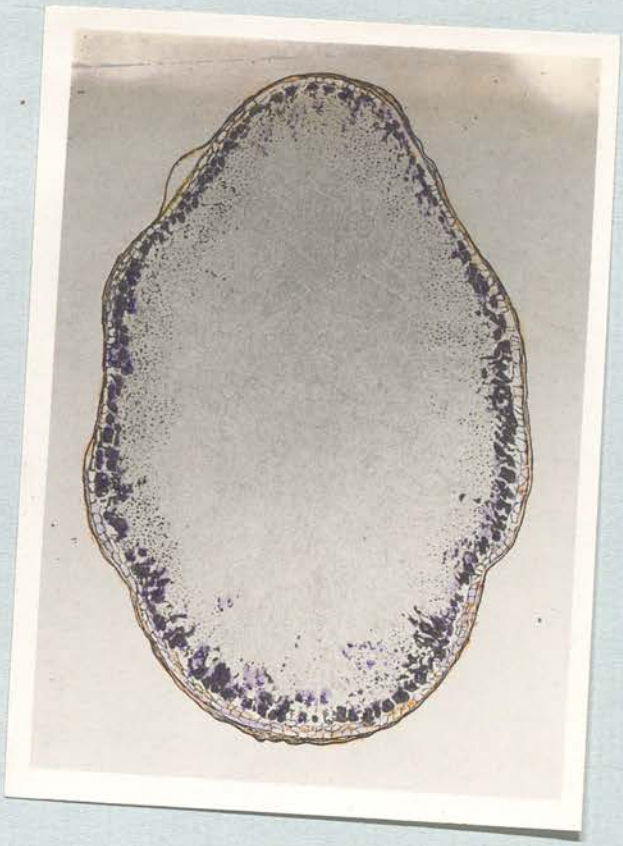
7) Bagan Serai.

This rice was parboiled in the Government mills at /

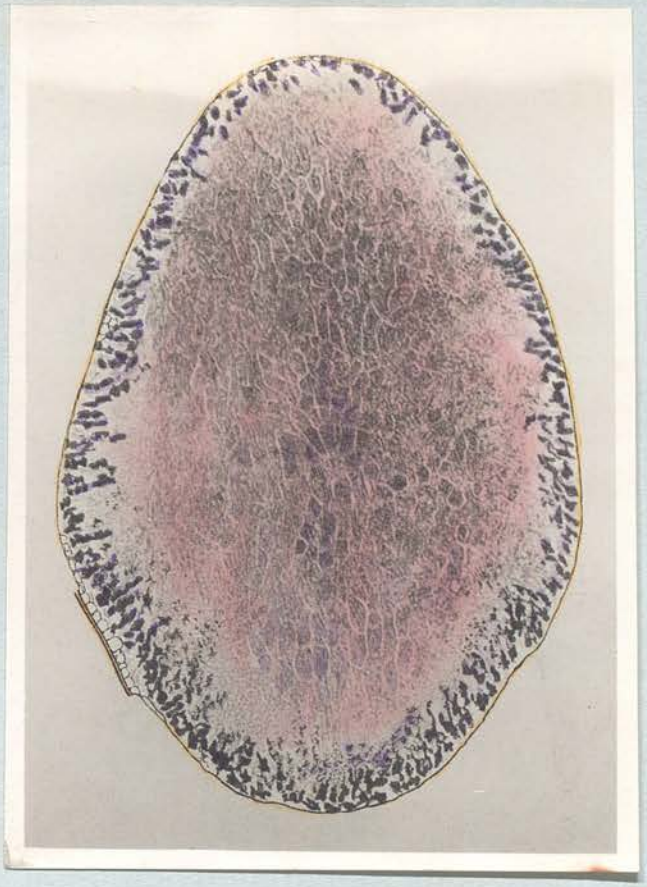
at Bagan Serai and was substituted for the Siam rice which had hitherto been the staple food of the S.S.R.N.V.R. ratings. The vitamin content of unhusked rice is disseminated through the endosperm by the method of "parboiling", and therefore subsequent decortication does not deprive it of its vitamin B to nearly the same extent as is the case with white "Siamese" rice.

Even when parboiled rice is used, it is believed that a further 100 I.U. approximately should be added daily to the diet in the form of vegetables and other foods with a high content of thiamin.

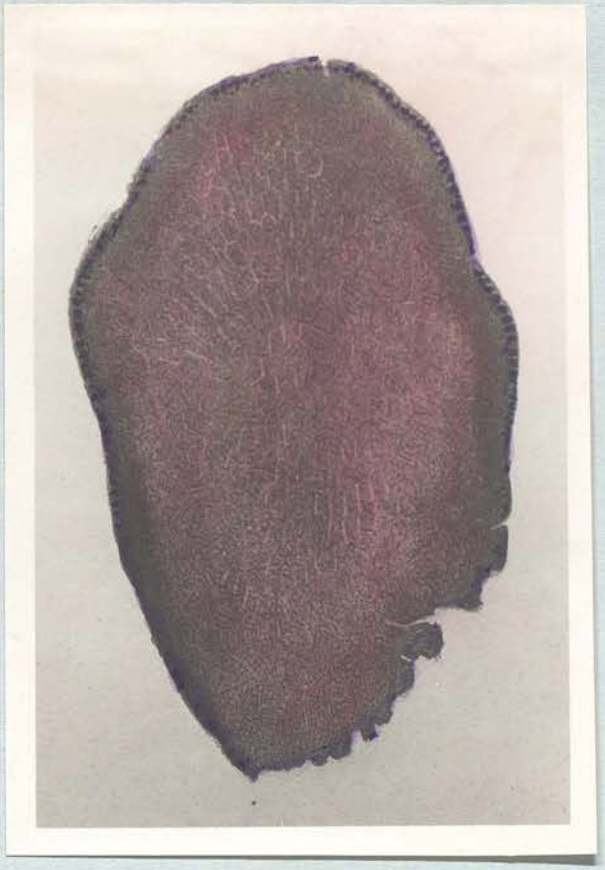
"When conditions are obtained for optimal production, it is found that there is no food crop of comparable nutritional value which can approach rice in the amount of food produced in a given area, and in its suitability as a food for man in the character and proportion of its ingredients", (136).



Transverse section of Padi (Husk removed).



Transverse section of Parboiled rice.



Transverse section of white (polished) rice.

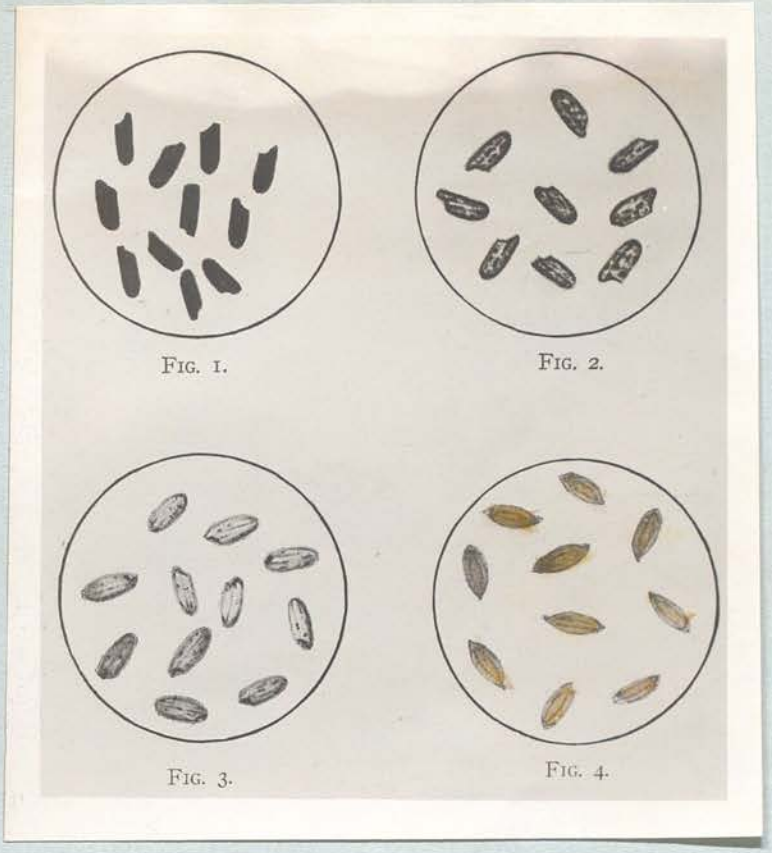


FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

Specimens of Rice stained with a solution of Gram's iodine.

Fig. 1. A highly milled or polished rice. The starch being completely exposed, stains uniformly, dark blue.

Fig. 2. An undermilled rice. The unstained areas shew where the adherent pericarp has protected the starch from the action of the iodine.

Fig. 3. A sample of undermilled rice that contains still more pericarp.

Fig. 4. The unhusked grain.

When the husks are removed by hand pounding, a rice similar to Fig. 2 or 3 is produced.

The vitamin B_1 content of Malayan foods is given in the following table taken from the figures of Leong (138), who used the "bradycardia" method of assay:-

A. CEREALS, PULSES AND THEIR PRODUCTS.

English and/or scientific names.	Local name.	I.U. of vit. B_1 per 100 grams.
Barley (Hordeum vulgare)	Beras belanda	20
Bread:-		
"bran"	Roti	30
"brown"	"	55
"Graham"	"	70
"rye"	"	58
"white"	"	8
"wholemeal"	"	63
Green dhall, dry (Phaseolus radiatus)	Kachang hijau	270
Red dhall (Cajanus indicus)	Dhall merah	140
Yellow dhall (Cajanus indicus) whole grain	Dhall kuning	160
Maize (Zea mays)	Jagong	37
Rice (Oryza sativa):-		
bran	Sekam	280
cargo	Beras merah	80
"	Oh Toh	100
"	Kim Chay	145
glutinous, white.	Pulut puteh	55
glutinous, black	Pulut hitam	100
husked, unpolished	Beras	140
parboiled	Beras kling	55
"	" "	100
"	" "	65
polishing	Dedak	780
Soya bean, black (Glycine hispida)	Kachang soya	245
Soya bean, white (Glycine soja):-		
whole bean	Kachang soya puteh	240

English and/or scientific names.	Local name.	I.U. of vit. B_1 per 100 grams.
curd, white	Tau hu huay	11
curd, hardened	Tau kua	43
Wheat (Triticum vulgare):	Gandum	
germ		620
flour	Atta	70
noodles	Mee	4
vermicelli	Mee	11
B. FRUITS.		
Banana (Musa Paradisiaca):-		
	Pisang embon	41
	Pisang kling	23
	Pisang mas	28
	Pisang merah	26
	Pisang rajah bulu	18
	Pisang tandok	13
(Gnetum gnemon)	Belinjau	56
(Phyllanthus emblica)	Buah melaka	10
(Zalacca edulis)	Buah salak	4
Carambola (Averrhoa carambola)	Belimbing manis	34
Date (Phoenix dactylifera)	Buah Khurma	13
Durian (Durio zibethinus):-		
"cake"	Durian "kuay"	50
fresh fruit	Durian	46
Grape (Vitis vinifera)	Buah anggor	19
Guava (Psidium guajava)	Jambu batu	52
Jack fruit (Artocarpus integra)	Nangka	26
Jack fruit (Artocarpus polyphemia)	Chempedak	52
(Eugenia aqua)	Jambu chili	14
(Spondias cytherea)	Kendondong	18
(Lansium domesticum)	Langsat	19
Lemon (Citrus limonis)	Limau susu	13

English and/or scientific names	Local name.	I.U. of vit. B_1 per 100 grams.
Lime (Citrus medica):-		
large	Limau nipis	8
small	Limau kesturi	13
Litchi nut (Litchi chinensis)	Lychee	5
Mango (Mangifera indica)	Mangga	18
Mangosteen (Garcinia mangostana)	Manggis	9
(Nephelium malaiense)	Matakuching	15
Papaya (Carica papaya)	Papaya	13
Passion fruit (Passinora laurifolia)	Buah susu	3
Persimmon (Diospyros kaki)	Samba (Buah samak)	26
Pineapple (Ananas comosa)	Nanas	27
Pomelo (Citrus maxima)	Limau bali	11
Raisin (vitis vinifera)	Anggor kering	32
(Baccaurea racemosa)	Rambai	5
(Nephelium lappaceum)	Rambutan	2
Rose apple (Eugenia malaccensis)	Jambu bol	11
Soursop (Anona muricata)	Durian blanda	40
Watermelon (Citrullus vulgaris)	Semangka	13
Water chestnut (Scirpus tuberosus)	Cheechang	18
Candle nut (Aleurites moluccana)	Buah keras	38
Cashew nut (Anacardium occidentale)	Biji gaju	220
Chestnut (Castanea vulgaris)	Kao lahk	70
Coconut (Cocos nucifera)	Kelapa isi	37
Gingelly seed (Sesamum indicum)	Bijan	390
Watermelon seed (Citrullus vulgaris):-		
black	Kuachi hitam	150
red	Kuachi merah	110

English and/or scientific names	Local name.	I.U. of vit. B_1 per 100 grams.
Peanut (Arachis hypogra)	Kachang goreng	235
D. GREENS, ROOTS AND OTHER VEGETABLES.		
Bamboo shoot (Dendrocalamus flagellifer)	Rebong	13
Bean sprout (Phaseolus radiatus)	Taugeh	29
Bitter gourd (Momordica charantia)	Peria	29
Bottle gourd (Lagenaria vulgaris)	Labu jantong	11
Breadfruit (Artocarpus incisa)	Sukun	15
Cabbage (Brassica oleracea)	Sayor kobis	34
Carrot (Daucus carota)	Lobak merah	40
Celery (Apium graveolens)	Daun seladeri	10
(Sauropus androgynus)	Chekup manis	51
Chillie (Capsicum annuum)	Chillie	41
Chinese cabbage leaf (Brassica chinensis)	Sayor puteh	32
" "	Kiam chye	0
(Brassica rapa varperviridis)	Chai sim	28
Cucumber (Cucumis sativus)	Timoon	8
Drumstick (Moringa pterygosperma)	Kelor	18
Egg plant (Solanum melongena)	Terong	30
Four angled bean (Psophocarpus tetragonolobus)	Kachang botor	21
French bean (Phaseolus vulgaris)	Kachang bunchis	24
(Coleus tuberosus)	Gemili	62
Hairy cucumber	Timoon bulu	18

English and/or scientific names.	Local name.	I.U. of vit. B_1 per 100 grams.
Jack fruit (Artocarpus polyphemia)	Chempedak	22
(Musa paradiasaca)	Jantong pisang	19
(Dolichos lablab)	Kachang kara	25
(Brassica albogabra)	Kai lan choy	48
(Ipomoea aquatica)	Kangkong	32
(Phaemeria speciosa)	Kantan	0
(Allium odorum)	Kuchai	40
Ladies finger (Abelmoschuses culentus)	Kachang bendi	34
Lettuce (Lactuca sativa)	Sayor salad	37
(Raphanus sativus)	Lobak	13
Loofah (Luffa acutangula)	Ketola	14
(Amaranthus sp.)	Mah si yin	20
Mint (Mentha sp.)	Daun pudina	69
Mustard leaf (Brassica juncea)	Sayor sawi	30
Onion, small (Allium fistulosum)	Bawang merah	18
Onion, large (Allium cepa)	Bawang besar	8
(Hydrocotyle asiatica)	Pegaga	30
Pepper, large green (Capsicum annum)	Lada	19
Potato (Solanum tuberosum)	Ubi gendang	40
Pumpkin (Cucurbita maxima)	Labu merah	23
(Zizania latifolia)	Rebong ayer	33
(Herspeslis monniera)	Sayor beremi	40
Spinach "Ceylon" (Basella rubra)	Sarn choy	25
Spinach, green (Amaranthus viridis)	Bayam puteh	32
Snake gourd (Tricosanthes anguina)	Ketola ular	13

English and/or scientific names.	Local name.	I.U. of vit. B_1 per 100 grams.
Spinach, red (Amaranthus gangeticus)	Bayam merah	14
Spring onion (Allium)	Daun bawang	6
String bean (Bigna sinensis)	Kachang panjang	30
Sweet potato (Ipomoea batatas)	Kledek merah	26
Sword bean (Canavalia ensiformis)	Kachang parang	25
Tapioca (Manihot utilissima)	Ubi kayu	26
Taro (Colocasia esculentum)	Keladi	36
Tomato (Lycopersicum esculentum)	Terong blanda	36
(Chrysanthemum coronarium)	Tong ho	25
Watercress (Nasturtium offinale)	Semanggi	43
White gourd (Benincasa hispida)	Tong kwah	5
(Brassica pekinensis)	Wong ngah pak	23
Yam bean (Pachyrhizus bulbosus)	Mangkwang	19
E. MILK AND MILK PRODUCTS.		
Butter	Mentega	30
Cheese	Keju	12
Milk, cow's	Susu, lembu	3
Milk powder	Susu tepong	73
F. EGGS.		
Duck egg, white	Puteh telor, itek	13
Duck egg, yolk	Kuning telor, itek	375
Hen egg, white	Puteh telor, ayam	0
Hen egg, yolk	Kuning telor, ayam	110
G. MEATS AND MEAT PRODUCTS.		
Bacon	Daging babi	260

English and/or scientific names	Local name.	I.U. of vit. B_1 per 100 grams.
Beef, lean	Daging lembu	45
Calf kidney	Buah pinggang, anak lembu	94
Mutton, lean	Daging kambing	23
Ox intestine	Tali perut lembu	13
Ox kidney	Buah pinggang lembu	125
Ox liver	Hati lembu	90
Ox tongue	Lidah lembu	56
Pig's liver	Hati babi	185
Pork, lean	Daging babi	260
H. FISHES AND OTHER MARINE PRODUCTS.		
Black trevally (Teutis sp.)	Dengkis	89
Crab	Ketam	92
Cuttle fish	Sotong	2
Dorab (Chirocentrus dorab)	Parang	41
Hilsa (Clupea sp.)	Terubok	13
Lobster	Udang galah	34
Oyster	Tiram	41
Prawn (Leander sp.)	Udang	24
Salt fish (Kurau) (Polynemus paradiseus)	Ikan asin (Kurau)	28
Sea-bream (Caesio kuning)	Delah	13
Sea-perch (Epinephelus sp.)	Kerapu	56
Shark (Sphyrna sp.)	Yu	10
Snapper (Lutianus roseus)	Ikan merah	58
Sole (Synaptura sp.)	Lidah	43
Spanish mackerel (Cybium paradiseus)	Tinggiri	19

English and/or scientific names.	Local name.	I.U. of vit. B_1 per 100 grams.
I. POULTRY AND GAME.		
Duck, muscle	Isi itek	130
Fowl, muscle	Isi ayam	50
Fowl, liver	Hati ayam	155
J. MISCELLANEOUS.		
Bird's nest	Sarang burong	17
Blachan	Blachan	30
Coriander (Coriandum sativum)	Ketumbar	0
Ginkgo seed (Ginkgo biloba)	Park kwoh	86
Honey	Ayer Labah	0
Lard	Minyak babi	30
Peanut oil (Arachis hypogoea)	Minyak kachang	26
Sago, pearl (Metroxylon sago)	Sagu	0
Sugar cane (Saccharum officinarum)	Tebu	4
Tamarind (Tamarindus indicus)	Assam jawa	25

"DRY COATING"

A condition affecting horses in the Tropics, due to vitamin deficiencies, most important of which is B_1.

Dry coating is referred to here, in view of the following:-

1) it is the most common, and the most dangerous condition affecting horses in the Tropics.

2) hitherto, no cure has yet been discovered.

3) I believe it to be the equine analogue of Beri-beri.

Unfortunately my experiments were brought to an abrupt and untimely conclusion by the outbreak of war in the Far East.

This condition affects horses only in hot, humid climates, especially India, Malaya and Java.

In Malaya, there were some 800 thoroughbreds, imported from both England and Australia; of these, approximately 25% were affected by dry-coating, - some worse than others.

When landed in Singapore, most of the horses were in reasonably good condition, and certainly none were dry-coated.

It was the practice to work a horse slowly through stages, taking about 3 - 6 months before galloping. Some of the animals developed a dry coat before they were even ready for racing and consequently had to be "spelled" at Cameron Highlands, one of our hill stations, at an altitude of between 3,000 and 4,000 feet. Here the climatic conditions were infinitely better. The horses were only walked, as there were no facilities for galloping them.

After about 3 months "up the hill" they would begin to /

to perspire quite freely again, and would then be sent down to Singapore, where after a few months they would be as bad as ever.

Character of the Condition.

A dry-coated horse is generally off his feed, and is often constipated. His eyes are listless, and he is lazy. It is commonly remarked that he is either "not doing well", or that he is "all tied up". The most marked feature is however, the entire absence of sweating even after fast work.

A healthy thoroughbred at the end of a race in the Tropics should perspire freely, and should pull up without blowing. In fact it was said that for a horse to be in really good condition after a race, one should be able to "hold a lighted candle in front of his nostrils": not so however, with a horse affected by dry-coating; when the race was finished, he would be "dry as a board", would blow, and pant, and on visiting the stables later one would see a thoroughly ill animal. A severe case would still be heaving and blowing 24 - 36 hours later, would get up and lie down every half hour, would be off his feed and look extremely uncomfortable.

If an animal was considered to be a bad case of dry-coating he would be barred from racing; nevertheless I have seen two horses drop dead during a race as a result of this condition.

At autopsy, these horses shewed dilatation

of /

of the heart, especially affecting the right side.

As the result of the similarity to beri-beri - breathlessness, weakness, anorexia, dilatation of the heart, and absence of sweating - it was thought that vitamin B_1 might be curative.

TREATMENT: Twenty thousand to forty thousand units of Berin (Glaxo Laboratories) were given by hypodermic injection daily for 14 days. During this time the horses were given medium work. After the first injection it was observed that the horses took their feed better, and at the end of the course looked in the "picture of condition".

After a hard morning's work, the marked improvement in breathing was at once obvious, and they did not seem to be distressed in any way. The "dry coat" however only shewed slight improvement.

It was considered justifiable to race one of these animals - Winchcliff. In his next three starts this horse was beaten by a short neck in his first, won his second by two lengths and his third by five lengths. He pulled up perfectly in all three but still was not perspiring quite as much as had been expected.

Was it possible then that a further factor was deficient?

Four horses - in addition to vitamin B1 had 60,000 units of vitamin A added to their feed, daily.

Four others were given nicotinic acid - 1,000 mgm. daily which was also added to their feed.

Sweating /

Sweating was improved in the former group, but not to the same extent as in the latter, in which it was considered cure was obtained.

The condition is therefore believed to be a vitamin deficiency disease occasioned by lack of vitamin B_1 and nicotinic acid. Vitamin A however, may also be involved.

Goodwin (1) reported as a manifestation of vitamin A deficiency in man "a marked reduction of sweating", and Rao (2) has remarked that in the same disorder the sweat glands do not appear to be secreting, and they are often plugged with keratinous material.

Guilbert and others (3) have experimented with horses on vitamin A deficient diets and found that the animals developed night blindness, rough coat, clouding of the cornea, and difficulty in breathing.

The following statement was found in a recent article by an American Veterinary Surgeon, (4).

"In a group of horses under our observation we were able to detect such symptoms as extreme nervousness, apparent irritation of the cutaneous nerve endings, anorexia, certain types of muscular paralysis (tying up), muscular fatigue (shivering), and the syndrome commonly described by horsemen as "not doing well" which we have felt might be of nutritional origin.....

Young horses with many of the symptoms above mentioned, that received a liberal amount of vitamin and /

and mineral supplement in the ration while training, showed marked improvement in condition.

We are more and more convinced that multiple vitamin deficiency in thoroughbreds in training is much more common than is generally supposed. Some of these horses received in addition to the oral administration intramuscular injections of liberal amounts of vitamin B complex in the form of Poly-B ampoules,

(thiamin hydrochlor	20 mg.
riboflavin	2 mg.
B_6	20 mg.
Nicotinic acid amide	20 mg.)

twice each week for 4 - 5 weeks. In every instance, the trainers were pleased with the improvement in the treated horses.

The administration of these vitamin numeral supplements was the only change in diet and treatment."

The thoroughbreds which I treated in Singapore for dry-coating were:-

Penthides

Last Chance

Winchcliff

Cimon

Artful Sailor

Thanks

Whiteface

Autumn Bride.

SUMMARY:

"Dry-Coating" is a disease affecting thoroughbreds and cavalry mounts in India, Malaya and Java.

It is characterised by

absence of sweating,

anorexia,

nervousness,

weakness,

fatigue,

extreme dyspnoea following "work",

dilatation of the heart.

An account is given of the cure of the condition in eight thoroughbreds - no other treatment has been curative or has even improved the condition.

It is the equine analogue of human beri-beri.

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SUMMARY.

The Etymology has been discussed, and it is considered that "beri-beri" derives its origin from the Cinghalese word "beri", which means "weakness".

Brief reference has been made to the early History of the condition, and to the discovery and isolation of vitamin B_1.

The "incubation period" is believed to be considerably less than the usually stated period of three months. On occasion, beri-beri may become manifest after only seven days on a deficient diet.

Many native subsist almost entirely on rice. It is unfortunate that they have been accustomed for many years to consider the highly-milled and polished rice as the best quality. Even if they wished to purchase under-milled rice, they could not do so under present conditions because the market is flooded with rice of the highly-milled variety. The basic diet is therefore often grossly deficient in vitamin B_1, and beri-beri frequently becomes manifest owing to some predisposing factor such as increased exertion, fatigue, any fever or debilitating illness, pregnancy, lactation, hyperthyroidism, or digestive disturbance.

It is considered that European women in the Tropics, when pregnant, occasionally develop mild beri-beri.

Beri-Beri is referred to as a syndrome which may shew different characteristics in different "epidemics".

Though /

Though fever is mentioned in certain text-books as a symptom of beri-beri, this is believed to be incorrect.

The following definition of beri-beri is suggested:-

"Beri-beri is a condition which occurs predominantly amongst the rice-eaters of India, and the Far East. It is a syndrome characterised by neurological lesions involving particularly the peripheral nerves, by oedema, or by acute congestive heart failure. In the main, it is occasioned by lack of vitamin B_1, but other factors, most important of which are the constituents of the vitamin B complex, are however, involved."

Physiology: For many years, it was thought that beri-beri resulted from a simple degeneration of the nervous system, consequent on deprivation of the "anti-neuritic" factor. How this degeneration is brought about has not yet been elucidated. There is, nevertheless, considerable evidence in favour of the theory that incompletely oxidised metabolic products are directly responsible. It has been known for some time that enzyme activity enters into each step in the oxidation of glucose in the human body, and that vitamin B_1 in the form of its pyrophosphoric ester (cocarboxylase) acts as a specific catalyst in the degradation of pyruvic acid.

Morbid Anatomy: Post-mortem studies have contributed little towards an understanding of the pathogenesis of the disease. The criteria for diagnosis at autopsy are:-

a) degeneration /

a) degeneration of the peripheral nerves,

b) absence of any other cause of death,

c) oedema,

and in shôshin -

d) dilatation of the right side of the heart, without evidence of organic cause.

Vitamin B_1 - deficiency has been discussed as it affects the nervous system, and the heart. A theory is advanced to account for the occurrence of oedema in some cases, and not in others. I believe it to be due to an associated deficiency - that of pyridoxin (vitamin B_6), or some other factor in the B_2 complex, as yet undifferentiated. The effects of thiamin-lack on the gastro-intestinal tract have been mentioned, and it is suggested that possibly the stunted growth of the Oriental races is connected with this vitamin deficiency.

Clinical Signs and Symptoms: It is considered that much of the literature, especially recent work, either devotes too little space to the characteristics of beri-beri, or does not give a true picture of the condition. An attempt has been made to describe fully the symptoms and signs as they occur at the present time in the Orient. It is impossible to summarise these effectively - reference must be made to the actual text.

It is most important to realise that beri-beri as it occurs in Malaya, affecting heavy rice-eaters, is very different /

different from experimental beri-beri in human beings on a more balanced diet.

Vitamin B_1 is considered to be of value in the treatment of Tropical Neurasthenia - one typical case has been mentioned as characteristic of the condition. It is believed that vitamin B_1 may also be of use in the treatment of Effort Syndrome.

There are at least three references in modern literature to the treatment of Landry's paralysis by vitamin B_1. It is considered that this form of therapy cannot benefit patients thus afflicted.

A brief description is given of the outbreak of beri-beri in the S.S.R.N.V.R., Singapore, April to July, 1941, and the steps taken to combat the disease. It was fortunate that beri-beri had been entirely eradicated some four months before the declaration of war by Japan.

The following associated deficiencies have been reported:-

a) Eczema of the scrotum - this condition did not respond to vitamin A and D, or to nicotinic acid. It was, however, cured by the administration of marmite and yeast tablets. It is considered that it may be due to lack of riboflavin or pantothenic acid.

b) Cheilosis, circum-corneal injection, and corneal vascularisation - this syndrome is due to riboflavin or pyridoxin deficiency.

c) Buccal, /

c) Buccal, lingual and mucous membrane abnormalities: the occurrence of glossitis and aphthous ulcers suggested a sub-pellagroid state; the condition responded to nicotinic acid therapy. Three cases of Vincent's Angina are reported, each of which was cured by nicotinic acid. It is not, nevertheless, considered that nicotinic acid is specific in this condition - some other factor is also implicated.

d) Hemeralopia: apart from vitamins A and C, the vitamin B complex is considered to play some part in the prevention and treatment of night-blindness.

e) Anaemias: an account is given of the occurrence of macrocytic anaemia in five British women who were pregnant, and in two ratings with beri-beri. All responded to Marmite.

A haemolytic form has been described for many years; this, I maintain, to be a false interpretation.

f) Abnormal conditions of the skin: dryness and roughness of the skin, together with an absence of sweating or "dry-coating" is described. It is similar to, though not identical with, the condition known as Phrynoderma, which is believed to be due mainly to a lack of vitamin A. The cases mentioned in this thesis responded to nicotinic acid therapy, and it is therefore possible that this vitamin may be found of value also in the treatment of Phrynoderma.

The Clinical Diagnosis of beri-beri has been discussed: the earliest symptoms are:-

a) indigestion,

b) "pins /

b) "pins and needles" affecting fingers and/or toes.

c) inability to perform any task involving extra expenditure of energy,

d) breathlessness,

e) palpitation,

f) oedema of the feet and ankles.

(Swelling of the feet and ankles affecting British women who are pregnant in the Tropics is believed to be often a sign of mild beri-beri.)

The following signs are important in arriving at a diagnosis:-

a) anaesthetic area over the anterior surface of the tibia,

b) hyperaesthesia of the calf muscles,

c) loss, firstly, of the ankle jerks, and later, of the knee reflexes,

d) oedema,

e) the gait, which is more commonly a "shuffle", than the so-called characteristic "steppage-gait",

f) enlargement of the right side of the heart,

g) cardiac murmurs.

Certain aids to diagnosis are described:-

1) determination of vitamin B_1 deficiency.

2) Volhard's diuresis test.

3) Aalsmeer's adrenalin test.

4) estimation of the amount of sweating.

5) Electrocardiograms.

6) /

6) X-rays.

7) Circulation time.

8) Exercise tests.

The literature regarding vitamin B_1 requirements of man has been analysed, and it indicates that the daily optimum is in the region of 700 I.U.; in other words, some 20 - 25 I.U. per 100 calories. Young children require more in proportion to their weight; pregnant and nursing women require from two to five times the minimum vitamin B_1 requirement (300 I.U.).

The conditions in which an extra amount of vitamin B_1 is indicated, have been tabulated. It is believed that following any debilitating illness in the tropics affecting Europeans and natives alike, vitamin B_1 and the B complex are of greater importance than iron, as a tonic.

Measures for the prevention of beri-beri in tropical countries have been suggested:-

a) education, and articles in the lay press,

b) popularisation of parboiled rice, and vitamin B_1 bread: introduction of "food yeast",

c) emphasis on the value of certain foods with a high vitamin-B_1 content,

d) instruction as to the preparation of rice and other foods.

The old Malayan cures have been mentioned for interest, and the modern lines of treatment indicated. Thiamin as we now know, is specific as a cure for the major symptoms /

symptoms of the condition. As, however, beri-beri is a syndrome, in which there are often associated deficiencies, the constituents of Marmite,which proved of great benefit in the treatment of the "other" manifestations of the condition, have been described in full.

The various types of rice used in Malaya have been remarked on, with indications as to the relative merits of the different varieties.

A brief reference has been made to "Dry-coating" in horses, as the condition is, I believe, analogous to human beri-beri, and as the work is entirely own conception. Curative measures have been indicated.

"And his fame went throughout all Syria; and they brought unto him all sick people that were taken with divers diseases and torments, and those which were possessed with devils, and those which were lunatick and those that had the palsy; and he healed them."

Matthew 4, 24.

Doctors can now cure the particular form of palsy called beri-beri; further, the condition can be easily prevented if certain salient facts are observed.

If we, British, are to be worthy of our colonies after the war, it is imperative that beri-beri, which still exacts such a toll of the native populations under our jurisdiction and care, should be eradicated.

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